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SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R) 1950-2006/Nov 03
         (c) format only 2006 Dialog
  File  55:Biosis Previews(R) 1993-2006/Oct W5
         (c) 2006 The Thomson Corporation
  File  34:SciSearch(R) Cited Ref Sci 1990-2006/Oct W5
         (c) 2006 The Thomson Corp
  File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
         (c) 2006 The Thomson Corp
  File 340:CLAIMS(R)/US Patent 1950-06/Nov 02
         (c) 2006 IFI/CLAIMS(R)
*File 340: IPCR/8 classification codes now searchable in 2006 records.
For important information about IC=index changes, see HELP NEWSIPCR.

      Set  Items  Description
      ---  -----  -----------
? s psma or (prostate(w)specific(w)membrane(w)antigen
>>>Unmatched parentheses
? s psma or (prostate(w)specific(w)membrane(w)antigen
>>>Unmatched parentheses
? s psma or (prostate(w)specific(w)membrane(w)antigen)
           1281  PSMA
         224323  PROSTATE
        2948259  SPECIFIC
        1601197  MEMBRANE
         914405  ANTIGEN
           1490  PROSTATE(W)SPECIFIC(W)MEMBRANE(W)ANTIGEN
      S1   1887  PSMA OR (PROSTATE(W)SPECIFIC(W)MEMBRANE(W)ANTIGEN)
? s recurren? or relaps?
         592559  RECURREN?
         174683  RELAPS?
      S2 727770  RECURREN? OR RELAPS?
? s s1 and s2
           1887  S1
         727770  S2
      S3    137  S1 AND S2
? s prostate
      S4 224323  PROSTATE
? s s3 and s4
            137  S3
         224323  S4
      S5    134  S3 AND S4
? s s5 and py<=2003
Processing
Processing
            134  S5
       47244967  PY<=2003
      S6     99  S5 AND PY<=2003
? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
      S7     57  RD  (unique items)
? s cancer? or malignan? or carcinoma
        1755440  CANCER?
         633901  MALIGNAN?
         955862  CARCINOMA
      S8 2672473  CANCER? OR MALIGNAN? OR CARCINOMA
? s s7 and s8
            57  S7
       2672473  S8
      S9     55  S7 AND S8
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? predict? or risk
>>>Invalid syntax at or near 'EDICT?'.
? s predict? or risk
         1673318  PREDICT?
         1808046  RISK
     S10 3253532  PREDICT? OR RISK
? s s9 and s10
              55  S9
         3253532  S10
     S11      19  S9 AND S10
? t s11/3,k,ab/1-19

 11/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2006 Dialog. All rts. reserv.

14640940   PMID: 14695135
  Correlation of primary tumor prostate-specific membrane
 antigen expression with disease recurrence in prostate
  ***cancer***  .
  Ross Jeffrey S; Sheehan Christine E; Fisher Hugh A G; Kaufman Ronald P;
Kaur Prabhjot; Gray Karen; Webb Iain; Gray Gary S; Mosher Rebecca;
Kallakury Bhaskar V S
  Departments of Pathology and Laboratory Medicine, Albany Medical College,
Albany, New York 12208, USA. rossj@mail.amc.edu
  Clinical cancer research - an official journal of the American
Association for Cancer Research (United States) Dec 15 2003, 9
 (17) p6357-62, ISSN 1078-0432--Print Journal Code: 9502500
  Publishing Model Print
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: MEDLINE; Completed
  PURPOSE: The restricted expression of the surface glycoprotein
prostrate-specific membrane antigen (PSMA) to normal prostate
 tissue, primary and metastatic prostate cancer (PCa), and the
neovasculature of various nonprostatic epithelial malignancies has
enabled targeting strategies for PCa treatment using anti-PSMA
antibodies. EXPERIMENTAL DESIGN: Using prostatectomy specimens,
immunohistochemical staining for PSMA (7E11 antibody) was performed
on formalin-fixed paraffin-embedded sections of 136 cases of PCa.
Cytoplasmic immunoreactivity was scored for intensity and distribution, and
results were correlated with tumor grade, pathological stage, DNA ploidy
status (Feulgen spectroscopy), and disease ***recurrence*** . ***PSMA***
mRNA expression in selected primary tumors and metastatic lesions was also
detected using in situ hybridization and autoradiography. RESULTS:
Generally, PCa cells expressed relatively increased levels of PSMA as
compared with benign elements. Among the PCa cases, increased (high)
  ***PSMA*** expression correlated with tumor grade (P = 0.030), pathological
stage (P = 0.029), aneuploidy (P = 0.010), and biochemical ***recurrence***
 (P = 0.001). The mean serum ***prostate*** -specific antigen level of 18.28
ng/ml at the time of diagnosis for the PSMA-overexpressing tumors was
significantly greater than the mean serum prostate-specific antigen
of 9.10 ng/ml for the non-PMSA-overexpressing group (P = 0.006). On
multivariate analysis, pathological stage (P = 0.018) and ***PSMA***
 expression (P = 0.002) were independent ***predictors*** of biochemical
  ***recurrence*** . ***PSMA*** protein overexpression in high-grade primary
PCa tumors and metastatic lesions also correlated with increased PSMA
mRNA expression levels using in situ hybridization and autoradiography.
CONCLUSIONS: This study demonstrates for the first time that overexpression
of PSMA in primary PCa correlates with other adverse traditional
prognostic factors and independently ***predicts*** disease outcome.
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Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate ***cancer*** .
... ***2003*** ,
PURPOSE: The restricted expression of the surface glycoprotein prostrate-specific membrane antigen (PSMA) to normal prostate tissue, primary and metastatic prostate cancer (PCa), and the neovasculature of various nonprostatic epithelial malignancies has enabled targeting strategies for PCa treatment using anti-PSMA antibodies. EXPERIMENTAL DESIGN: Using prostatectomy specimens, immunohistochemical staining for PSMA (7E11 antibody) was performed on formalin-fixed paraffin-embedded sections of 136 cases of PCa...

...results were correlated with tumor grade, pathological stage, DNA ploidy status (Feulgen spectroscopy), and disease ***recurrence*** . ***PSMA*** mRNA expression in selected primary tumors and metastatic lesions was also detected using in situ hybridization and autoradiography. RESULTS: Generally, PCa cells expressed relatively increased levels of PSMA as compared with benign elements. Among the PCa cases, increased (high) ***PSMA*** expression correlated with tumor grade (P = 0.030), pathological stage (P = 0.029), aneuploidy (P = 0.010), and biochemical ***recurrence*** (P = 0.001). The mean serum ***prostate*** -specific antigen level of 18.28 ng/ml at the time of diagnosis for the PSMA-overexpressing tumors was significantly greater than the mean serum prostate-specific antigen of 9.10 ng/ml for the non-PMSA-overexpressing group (P = 0.006). On multivariate analysis, pathological stage (P = 0.018) and ***PSMA*** expression (P = 0.002) were independent ***predictors*** of biochemical ***recurrence*** . ***PSMA*** protein overexpression in high-grade primary PCa tumors and metastatic lesions also correlated with increased PSMA mRNA expression levels using in situ hybridization and autoradiography. CONCLUSIONS: This study demonstrates for the first time that overexpression of PSMA in primary PCa correlates with other adverse traditional prognostic factors and independently ***predicts*** disease outcome.
...Descriptors: biosynthesis--BI; *Glutamate Carboxypeptidase II --biosynthesis--BI; *Prostatic Neoplasms--metabolism--ME; *Prostatic Neoplasms--pathology--PA; *Recurrence

11/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13923821 PMID: 12230621
Can the reverse transcriptase-polymerase chain reaction for prostate specific antigen and prostate specific membrane antigen improve staging and predict biochemical recurrence?
Adsan O; Cecchini M G; Bisoffi M; Wetterwald A; Klima I; Danuser H-J; Studer U E; Thalmann G N
Urology Research Laboratory, Department of Urology, University of Berne, Switzerland.
BJU international (England) Oct 2002, 90 (6) p579-85, ISSN 1464-4096--Print Journal Code: 100886721
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: To evaluate the perioperative gene-specific primed nested reverse transcription-polymerase chain reaction (RT-PCR) for prostate -specific antigen (PSA) and prostate-specific membrane antigen (PSMA) for staging patients undergoing radical prostatectomy and ***predicting*** biochemical ***recurrence*** . PATIENTS

AND METHODS: In 80 consecutive patients undergoing radical prostatectomy for prostate cancer , blood samples were drawn before, during and 1 and 7 days after removing the ***prostate*** . After buffy coat and mRNA extraction, gene-specific primed nested RT-PCR was performed for PSA, PSMA and glyceraldehyde-3-phosphate dehydrogenase mRNA, and Southern blot analysis of the PCR reaction. RESULTS: The sensitivity of gene-specific RT-PCR to detect tumour cells was comparable with random primed RT-PCR. In the 80 patients the stage distribution was pT1 in two (2.5%), pT2 in 30 (37.5%) and > or = pT3 in 48 (60%); the nodal status was pN0 in 57 (71%), pN1 in 11 (14%) and pN2 in 12 (15%). The gene-specific RT-PCR reaction for PSA and PSMA was positive in no patients with pT1, 11 (37%) with pT2 and 23 (48%) with stage > or = pT3 disease. The result for PSA was positive in 12 (52%) and for PSMA in 11 (48%) of those with positive nodal status. Neither gene-specific RT-PCR for PSA or ***PSMA*** was able to ***predict*** organ-confined disease (P > 0.5). After a median (range) follow-up of 37 (11-67) months a biochemical recurrence was predicted in 65% of patients by preoperative RT-PCR for both PSA and PSMA , with a sensitivity, specificity, positive and negative predictive value of 58%, 80%, 87% and 47%, respectively; the assay after surgery predicted a recurrence in 73%, with respective values of 68%, 84%, 84% and 57%. CONCLUSIONS: Gene-specific primed nested RT-PCR for PSA and PSMA is a sensitive and simple assay; it might add substantial information for tumour staging in individual patients. RT-PCR before surgery allows the ***prediction*** of ***recurrence*** in 65% of cases and after surgery in 73%.

Can the reverse transcriptase-polymerase chain reaction for prostate specific antigen and prostate specific membrane antigen improve staging and predict biochemical recurrence?

... ***2002*** ,

... evaluate the perioperative gene-specific primed nested reverse transcription-polymerase chain reaction (RT-PCR) for prostate -specific antigen (PSA) and prostate-specific membrane antigen (PSMA) for staging patients undergoing radical prostatectomy and ***predicting*** biochemical ***recurrence*** . PATIENTS AND METHODS: In 80 consecutive patients undergoing radical prostatectomy for prostate cancer , blood samples were drawn before, during and 1 and 7 days after removing the ***prostate*** . After buffy coat and mRNA extraction, gene-specific primed nested RT-PCR was performed for PSA, PSMA and glyceraldehyde-3-phosphate dehydrogenase mRNA, and Southern blot analysis of the PCR reaction. RESULTS...

...14%) and pN2 in 12 (15%). The gene-specific RT-PCR reaction for PSA and PSMA was positive in no patients with pT1, 11 (37%) with pT2 and 23 (48%) with stage > or = pT3 disease. The result for PSA was positive in 12 (52%) and for ***PSMA*** in 11 (48%) of those with positive nodal status. Neither gene-specific RT-PCR for PSA or PSMA was able to ***predict*** organ-confined disease (P > 0.5). After a median (range) follow-up of 37 (11-67) months a biochemical recurrence was predicted in 65% of patients by preoperative RT-PCR for both PSA and PSMA, with a sensitivity, specificity, positive and negative predictive value of 58%, 80%, 87% and 47%, respectively; the assay after surgery predicted a recurrence in 73%, with respective values of 68%, 84%, 84% and 57%. CONCLUSIONS: Gene-specific primed nested RT-PCR for PSA and PSMA is a sensitive and simple assay; it might add substantial information for tumour staging in individual patients. RT-PCR before surgery allows the prediction of recurrence in 65% of cases and after surgery in 73%.

Descriptors: *Neoplasm Recurrence, Local--diagnosis--DI; * Prostate-Specific Antigen--blood--BL; *Prostatic Neoplasms--diagnosis --DI; Blotting, Southern; Humans; Neoplasm Recurrence, Local--blood --BL; Prostatectomy--methods--MT; Prostatic Neoplasms--blood--BL;

Prostatic Neoplasms--surgery--SU; Research...
Enzyme No.: EC 3.4.21.77 (***Prostate*** -Specific Antigen)
Chemical Name: Prostate-Specific Antigen

11/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11/07

13859836 PMID: 12149293

Preoperative combined nested reverse transcriptase polymerase chain reaction for prostate-specific antigen and prostate-specific membrane antigen does not correlate with pathologic stage or biochemical failure in patients with localized ***prostate*** ***cancer*** undergoing radical prostatectomy.

Thomas John; Gupta Manjula; Grasso Ying; Reddy Chandana A; Heston Warren D; Zippe Craig; Dreicer Robert; Kupelian Patrick A; Brainard Jennifer; Levin Howard S; Klein Eric A

Urological Institute, Taussig Cancer Center, Lerner Research Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA.

Journal of clinical oncology - official journal of the American Society of Clinical Oncology (United States) Aug 1 2002, 20 (15) p3213-8
, ISSN 0732-183X--Print Journal Code: 8309333
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

PURPOSE: We report a prospective study examining the ability of preoperative nested reverse transcriptase polymerase chain reaction (RT-PCR) for prostate-specific antigen (PSA) and prostate-specific membrane antigen (PSM) to predict pathologic stage and biochemical recurrence in patients with clinically localized prostate cancer treated with radical prostatectomy. PATIENTS AND METHODS: One hundred forty-one patients were entered onto the study. Preoperative evaluation included clinical T stage, serum PSA, biopsy Gleason score, and serum RT-PCR for PSA/PSM. Univariate and multivariate logistic regression models, Kaplan-Meier estimates, and Cox proportional hazards modeling were used to identify predictors of pathologic stage and biochemical failure. RESULTS: Seventy-three patients (51.8%) were RT-PCR positive for PSA, PSM, or both. In the multivariate logistic regression model, only initial PSA was an independent predictor of pathologic stage as defined by organ-confined disease (odds ratio [OR], 1.06; 95% confidence interval [CI], 1.00 to 1.13; P =.026) or organ-/specimen-confined disease (OR, 1.09; 95% CI, 1.02 to 1.16; P =.009). Overall Kaplan-Meier biochemical ***relapse*** -free survival (bRFS) was 85% at 59 months. Multivariate analysis of ***predictors*** for bRFS with the Cox proportional hazards model indicated that only initial PSA (OR, 1.05; 95% CI, 1.02 to 1.09; P =.004) and biopsy Gleason score (OR, 3.57; 95% CI, 1.37 to 9.58; P =.009) were independent ***predictors*** of biochemical failure. RT-PCR status did not ***predict*** pathologic stage or biochemical failure. Repeat analysis excluding 27 patients who received preoperative androgen-deprivation therapy did not change the results. CONCLUSION: Combined nested RT-PCR for PSA and PSM is not an independent predictor of pathologic stage or biochemical failure in patients with localized ***prostate*** ***cancer*** undergoing radical prostatectomy. This assay has no clinical utility in this patient population.

Preoperative combined nested reverse transcriptase polymerase chain reaction for prostate-specific antigen and prostate-specific membrane antigen does not correlate with pathologic stage or biochemical failure in patients with localized ***prostate*** ***cancer*** undergoing radical prostatectomy.

... ***2002*** ,
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... the results. CONCLUSION: Combined nested RT-PCR for PSA and PSM is not an independent predictor of pathologic stage or biochemical failure in patients with localized prostate cancer undergoing radical prostatectomy. This assay has no clinical utility in this patient population.

Descriptors: *Antigens, Surface; *Carboxypeptidases--blood--BL; * Prostate-Specific Antigen--blood--BL; *Prostatic Neoplasms--blood--BL ; *Prostatic Neoplasms--pathology--PA; *Reverse Transcriptase Polymerase ...
; Disease-Free Survival; Glutamate Carboxypeptidase II; Humans; Logistic Models; Neoplasm Recurrence, Local; Neoplasm Staging; Predictive Value of Tests; Preoperative Care; Proportional Hazards Models; Prospective Studies; Prostatectomy; Prostatic Neoplasms--surgery --SU

...Enzyme No.: II); EC 3.4.17.21 (glutamate carboxypeptidase II, human) ; EC 3.4.21.77 (***Prostate*** -Specific Antigen)

Chemical Name: Antigens, Surface; Carboxypeptidases; Glutamate Carboxypeptidase II; glutamate carboxypeptidase II, human; Prostate -Specific Antigen

11/3,K,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13832872 PMID: 12114876

The role of (111)In Capromab Pendetide (Prosta-ScintR) immunoscintigraphy in the management of ***prostate*** ***cancer*** .

Freeman L M; Krynyckyi B R; Li Y; Korupulu G; Saleemi K; Haseman M K; Kahn D

Department of Nuclear Medicine, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York 10467, USA. Lfreeman@montefiore.org

quarterly journal of nuclear medicine - official publication of the Italian Association of Nuclear Medicine (AIMN) and the International

Association of Radiopharmacology (IAR) (Italy) Jun 2002, 46 (2) p131-7, ISSN 1125-0135--Print Journal Code: 9512274
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
(111)In Capromab Pendetide (ProstaScintR) is a whole murine antibody that is reactive with prostate specific membrane antigen (PSMA), a glycoprotein on the surface of normal and abnormal ***prostate*** epithelium. It has proven to be of great value in assisting management decisions in prostate cancer patients who initially present with high risk for metastatic spread, or who develop a picture of ***recurrent*** disease after surgery or radiation therapy. Patterns of metastatic lymphatic spread have correlated well with autopsy reports in the literature. Unfortunately, other imaging study and/or histologic confirmation of scintigraphic findings has been difficult to obtain. Prostascint's role in ***predicting*** durable complete response (DCR) in postoperative patients having salvage radiotherapy to their ***prostate*** fossa is very promising. Further investigative work in larger patient populations is needed to confirm these early results.

The role of (111)In Capromab Pendetide (Prosta-ScintR) immunoscintigraphy in the management of ***prostate*** ***cancer*** .
... ***2002*** ,
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11/3,K,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13346170 PMID: 11506953
Abnormal E-cadherin expression and prostate cell blood dissemination as markers of biological ***recurrence*** in ***cancer*** .
Loric S; Paradis V; Gala J L; Berteau P; Bedossa P; Benoit G; Eschwege P
Biochemistry A Laboratory, Saint-Antoine AP-HP University Hospital, 184 ru du Faubourg, Saint-Antoine, 75012 Paris, France. slyvain.loric@sat.ap-hop-paris.fr
European journal of cancer (Oxford, England - 1990) (England) Aug 2001, 37 (12) p1475-81, ISSN 0959-8049--Print Journal Code: 9005373
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Until now, no molecular parameter has been available for predicting the metastatic potential of prostate tumours, which leaves their outcome uncertain despite an apparent benign histology or early stage. Abnormal expression of adhesion molecules, such as E-cadherin, can be

contributing factors for increased invasiveness and metastatic potential. Histological analysis for E-cadherin expression was carried out on paraffin-embedded tumour tissues. Tumour metastatic potential was indirectly evaluated by detecting circulating prostate cells (CPC), using reverse transciptase-polymerase chain reaction (RT-PCR) and prostate-specific membrane antigen (PSMA) as
a target. Patients were followed-up for a median of 14 months (range 10--19 months) after surgery with serum prostate-specific antigen (PSA) level measurement. Interestingly, 23 of 44 localised tumours exhibited aberrant E-cadherin expression. Prior to primary surgery, ***PSMA*** RT-PCR detected the spread of ***prostate*** cells to the blood in 24 patients. Statistical analysis showed that abnormal E-cadherin expression in the tumours was the only variable that was independently correlated with ***prostate*** cell dissemination in the blood (P<0.0001). In logistic regression analysis, abnormal E-cadherin expression was a significant independent ***predictor*** for a later biological ***relapse*** . This impaired adhesion status was clearly correlated with a haematogenous spread of the primary tumour cells. It could therefore be an objective way to restrict the indications for radical surgery to patients not presenting with this feature.

Abnormal E-cadherin expression and prostate cell blood dissemination as markers of biological ***recurrence*** in ***cancer*** .
... ***2001*** ,
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...; Studies; Glutamate Carboxypeptidase II; Humans; Immunohistochemistry --methods--MT; Middle Aged; Neoplasm Circulating Cells--metabolism--ME; Prostate-Specific Antigen--blood--BL; Recurrence; Regression Analysis; Research Support, Non-U.S. Gov't; Reverse Transcriptase Polymerase Chain Reaction
...Enzyme No.: II); EC 3.4.17.21 (glutamate carboxypeptidase II, human) ; EC 3.4.21.77 (***Prostate*** -Specific Antigen)
Chemical Name: Antigens, Surface; Cadherins; Tumor Markers, Biological; Carboxypeptidases; Glutamate Carboxypeptidase II; glutamate carboxypeptidase II, human; Prostate-Specific Antigen

11/3,K,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13115898 PMID: 11272670
Utility of capromab pendetide (ProstaScint) imaging in the management of

prostate ***cancer*** .
Rosenthal S A; Haseman M K; Polascik T J
Division of Radiation Oncology, Radiological Associates of Sacramento Medical Group, Inc., California 95815, USA.
Techniques in urology (United States) Mar 2001, 7 (1) p27-37, ISSN 1079-3259--Print Journal Code: 9508161
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

11/4/02

PURPOSE: Capromab pendetide (ProstaScint) is an indium In 111 ((111)In)-labeled monoclonal antibody to prostate-specific membrane antigen (PSMA) used to image prostate ***cancer*** . The appropriate techniques for obtaining images with this modality and the appropriate clinical indications for this study are in the process of being optimized. MATERIALS AND METHODS: From 1994 to 2000, 631 monoclonal antibody imaging studies with (111)In capromab pendetide were performed. The accuracy and utility of this modality in the primary staging of patients with disease at high risk of metastasis and patients with ***recurrent*** or residual disease after primary therapy were evaluated. RESULTS: In high-risk patients evaluated for risk of lymph node metastases prior to pelvic lymph node dissection, capromab pendetide imaging was found to have a positive predictive value (PPV) of 62%, negative predictive value (NPV) of 72%, sensitivity of 62%, and specificity of 72%. In patients evaluated with capromab pendetide imaging for prostatic fossa recurrence using prostatic fossa needle biopsy as the gold standard, capromab pendetide imaging was found to have a PPV of 50%, NPV of 70%, sensitivity of 49%, and specificity of 71%. CONCLUSIONS: The sensitivity and NPV of (111)In capromab pendetide imaging are better than those of computed tomography and magnetic resonance imaging for detection of soft-tissue and nodal metastases from prostate ***cancer*** . The utility of this modality has been demonstrated in the primary staging of patients with disease at high ***risk*** of metastasis. Patients with recurrent or residual disease after primary therapy also may benefit from capromab pendetide imaging prior to selection of salvage therapy. Innovative methods for the use of capromab pendetide imaging in radiation therapy treatment planning are under development.

Utility of capromab pendetide (ProstaScint) imaging in the management of ***prostate*** ***cancer*** .
... ***2001*** ,

PURPOSE: Capromab pendetide (ProstaScint) is an indium In 111 ((111)In)-labeled monoclonal antibody to prostate-specific membrane antigen (PSMA) used to image prostate ***cancer*** . The appropriate techniques for obtaining images with this modality and the appropriate clinical indications for...

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recurrent or residual disease after primary therapy also may benefit from capromab pendetide imaging prior to...

11/3,K,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12796086 PMID: 10906737
Value of reverse transcription polymerase chain reaction assay in pathological stage T3N0 ***prostate*** ***cancer*** .
Okegawa T; Noda H; Kato M; Miyata A; Nutahara K; Higashihara E
Department of Urology, Kyorin University School of Medicine, Mitaka, Tokyo, Japan.
Prostate (UNITED STATES) Aug 1 2000, 44 (3) p210-8, ISSN 0270-4137--Print Journal Code: 8101368
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND: We tested the ability of the nested reverse transcription polymerase chain reaction (RT-PCR) assay to detect signs of biochemical recurrence of prostate cancer in the lymph nodes and peripheral blood of patients with pT3N0 ***prostate*** ***cancer*** . METHODS: Using lymph nodes and pre- and postoperative peripheral blood dissected from 30 patients with pT3N0 prostate cancer treated by radical prostatectomy, we used RT-PCR for prostate-specific membrane antigen (PSM) and serum prostate -specific antigen (PSA) to determine the presence of ***prostate*** ***cancer*** . Results of the nested RT-PCR assay were compared with pathological stages and biochemical ***recurrence*** . RESULTS: Two of 13 patients with capsular penetration (15%), 6 of 10 patients with invasion of seminal vesicles (60%), and 3 of 7 patients with a positive surgical margin (43%) were RT-PCR-positive for PSM and/or PSA in the lymph nodes. Results of preoperative RT-PCRs of peripheral blood for PSM and for PSA significantly differed between positive and negative results of RT-PCR in lymph nodes (P < 0.001 and P < 0.001, respectively). Results of postoperative RT-PCRs of peripheral blood for PSM and for PSA also significantly different between positive and negative results of RT-PCR in lymph nodes (P = 0.011 and P = 0.001, respectively). Nine of 11 patients with positive nested RT-PCR for PSM and/or PSA in the lymph nodes (82%) experienced biochemical ***recurrence*** . Significant difference in Kaplan-Meier ***recurrence*** -free actuarial curves was noted between patients who nested positive and negative on RT-PCR in the lymph nodes, pre- and postoperative peripheral blood, biopsy and prostatectomy Gleason score, and preoperative PSA values. In multivariate analysis, biopsy and prostatectomy Gleason score (P = 0.026, P = 0.020, respectively), pre- and postoperative RT-PCR for PSM in peripheral blood (P = 0.030 and P = 0.040, respectively), and RT-PCR for PSM in lymph nodes (P = 0.035) were independent prognostic factors. CONCLUSIONS: Nested RT-PCR assay of the lymph nodes or peripheral blood significantly ***predicted*** biochemical ***recurrence*** after surgery. It may help identify patients at risk for recurrence and progression of ***prostate*** ***cancer*** . Copyright 2000 Wiley-Liss, Inc.

Value of reverse transcription polymerase chain reaction assay in pathological stage T3N0 ***prostate*** ***cancer*** .
... ***2000*** ,
... the nested reverse transcription polymerase chain reaction (RT-PCR) assay to detect signs of biochemical recurrence of prostate cancer in the lymph nodes and peripheral blood of patients with pT3N0 ***prostate*** ***cancer*** . METHODS: Using lymph nodes and pre- and postoperative peripheral blood dissected from 30 patients with pT3N0

prostate cancer treated by radical prostatectomy, we used RT-PCR for prostate-specific membrane antigen (PSM) and serum prostate-specific antigen (PSA) to determine the presence of ***prostate*** ***cancer*** . Results of the nested RT-PCR assay were compared with pathological stages and biochemical ***recurrence*** . RESULTS: Two of 13 patients with capsular penetration (15%), 6 of 10 patients with invasion...

... nested RT-PCR for PSM and/or PSA in the lymph nodes (82%) experienced biochemical ***recurrence*** . Significant difference in Kaplan-Meier recurrence -free actuarial curves was noted between patients who nested positive and negative on RT-PCR...

... prognostic factors. CONCLUSIONS: Nested RT-PCR assay of the lymph nodes or peripheral blood significantly predicted biochemical ***recurrence*** after surgery. It may help identify patients at ***risk*** for ***recurrence*** and progression of ***prostate*** ***cancer*** .

Descriptors: *Antigens, Surface; *Carboxypeptidases--analysis--AN; *Neoplasm Recurrence, Local--pathology--PA; *Prostate --pathology--PA; *Prostate-Specific Antigen--analysis--AN; *Prostatic Neoplasms--pathology--PA...; Glutamate Carboxypeptidase II; Humans; Lymph Nodes--chemistry--CH; Lymph Nodes--pathology--PA; Middle Aged; Neoplasm Recurrence, Local--blood--BL; Neoplasm Recurrence, Local --diagnosis--DI; Predictive Value of Tests; Proportional Hazards Models; Prostate--chemistry--CH; Prostate-Specific Antigen --blood--BL; Prostate-Specific Antigen--genetics--GE; Prostatic Neoplasms--blood--BL; Prostatic Neoplasms--diagnosis--DI; RNA, Neoplasm --chemistry...

...Enzyme No.: II); EC 3.4.17.21 (glutamate carboxypeptidase II, human) ; EC 3.4.21.77 (***Prostate*** -Specific Antigen)

Chemical Name: Antigens, Surface; DNA, Neoplasm; RNA, Neoplasm; Carboxypeptidases; Glutamate Carboxypeptidase II; glutamate carboxypeptidase II, human; Prostate-Specific Antigen

11/3,K,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12656008 PMID: 10737491

Detection of micrometastatic prostate cancer cells in the lymph nodes by reverse transcriptase polymerase chain reaction is predictive of biochemical recurrence in pathological stage T2

prostate ***cancer*** .

Okegawa T; Nutahara K; Higashihara E

Department of Urology, Kyorin University School of Medicine, Mitaka, Tokyo, Japan.

Journal of urology (UNITED STATES) Apr 2000, 163 (4) p1183-8, ISSN 0022-5347--Print Journal Code: 0376374

Publishing Model Print; Comment in J Urol. 2000 Apr;163(4) 1189-90; Comment in PMID 10737492

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

PURPOSE: We evaluated whether detecting prostate cancer cells by the nested reverse transcriptase-polymerase chain reaction (RT-PCR) in lymph nodes has predictive value for serum prostate specific antigen (PSA) recurrence in patients undergoing radical prostatectomy. MATERIALS AND METHODS: We assessed the presence of prostate cancer cells by RT-PCR for prostate

specific membrane antigen and PSA assay in lymph nodes dissected from 38 patients with localized prostate cancer treated with radical prostatectomy. The results of nested RT-PCR assay were compared with biochemical ***recurrence*** . RESULTS: Nested RT-PCR was positive in the lymph nodes of 2 of 18 patients (11%) with stage pT2a and 5 of 20 (25%) with stage pT2b disease. All 7 patients had biochemical ***recurrence*** . We noted a significant difference in the Kaplan-Meier recurrence -free actuarial probability curve in those with positive and negative nested RT-PCR results for prostate specific membrane antigen, PSA and prostate specific ***membrane*** ***antigen*** -PSA in the lymph nodes (p = 3.02x10(-7), 2.23x10(-7) and 3.02x10(-7), respectively). Multivariate analysis of serum PSA, Gleason score and preoperative RT-PCR assay in peripheral blood showed that nested RT-PCR for prostate specific membrane antigen, PSA and prostate specific membrane antigen-PSA in the lymph nodes were independent predictors of ***recurrence*** (p = 0.0089, 0.0075 and 0.0089, respectively). CONCLUSIONS: Nested RT-PCR of the lymph nodes may be a useful pretreatment prognostic test for patients undergoing radical prostatectomy. Further research is necessary using a much larger number of patients with a longer followup.

Detection of micrometastatic prostate cancer cells in the lymph nodes by reverse transcriptase polymerase chain reaction is predictive of biochemical recurrence in pathological stage T2 ***prostate*** ***cancer*** .

... ***2000*** ,

PURPOSE: We evaluated whether detecting prostate cancer cells by the nested reverse transcriptase-polymerase chain reaction (RT-PCR) in lymph nodes has predictive value for serum prostate specific antigen (PSA) recurrence in patients undergoing radical prostatectomy. MATERIALS AND METHODS: We assessed the presence of prostate cancer cells by RT-PCR for prostate specific membrane antigen and PSA assay in lymph nodes dissected from 38 patients with localized prostate cancer treated with radical prostatectomy. The results of nested RT-PCR assay were compared with biochemical ***recurrence*** . RESULTS: Nested RT-PCR was positive in the lymph nodes of 2 of 18 patients...

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... score and preoperative RT-PCR assay in peripheral blood showed that nested RT-PCR for prostate specific membrane antigen, PSA and prostate specific membrane antigen-PSA in the lymph nodes were independent predictors of ***recurrence*** (p = 0.0089, 0.0075 and 0.0089, respectively). CONCLUSIONS: Nested RT-PCR of the...

; Aged; Humans; Lymphatic Metastasis; Middle Aged; Neoplasm Recurrence, Local--blood--BL; Neoplasm Recurrence, Local --epidemiology--EP; Neoplasm Staging; Predictive Value of Tests; Prognosis; Prostate-Specific Antigen--blood--BL; Prostatectomy; Prostatic Neoplasms--blood--BL; Prostatic Neoplasms--surgery--SU; Reverse Transcriptase...

Enzyme No.: EC 3.4.21.77 (***Prostate*** -Specific Antigen)

Chemical Name: Prostate-Specific Antigen

11/3,K,AB/9 (Item 9 from file: 155)

12532268 PMID: 10477909

Circulating levels of interleukin-6 in patients with hormone refractory ***prostate*** ***cancer*** .

Drachenberg D E; Elgamal A A; Rowbotham R; Peterson M; Murphy G P
Pacific Northwest Cancer Foundation/Northwest Hospital, Seattle, Washington.

Prostate (UNITED STATES) Oct 1 1999, 41 (2) p127-33, ISSN 0270-4137--Print Journal Code: 8101368
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

BACKGROUND: Interleukin-6 (IL-6) is a cytokine that plays a central role in host defense due to its wide range of immune and hematopoietic activities. It is found in high levels in human ejaculate, and has recently been found to regulate prostate-specific protein expression in prostate cancer cells through nonsteroidal activation of the androgen receptor. IL-6 may be a candidate mediator of morbidity in patients with metastatic disease. We attempted to evaluate the potential of circulating IL-6 levels as a marker of disease progression. MATERIALS AND METHODS Serum IL-6, prostate specific antigen (PSA), percent free PSA (%fPSA), and prostate-specific membrane antigen (PSMA) were measured using commercially available assays in 407 men, including 15 controls. The rest of the study population had clinical or histologic evidence of prostate diseases, including 41 patients with chronic prostatitis, 167 with benign prostatic hyperplasia (BPH), 8 with high-grade prostatic intraepithelial neoplasia (PIN), 88 with localized prostate cancer, 22 with local recurrence after treatment of primary tumor, 4 with advanced untreated disease (nodal or bony metastases), 23 with advanced hormone dependent disease, and 39 with advanced hormone refractory disease (PSA > 1.0 ng/ml while on hormone treatment and/or evidence of disease progression). None had history of concurrent ***malignancy*** or acute inflammatory condition. Kruskal-Wallis analysis of variance and Spearman's correlation analysis were used for statistical analyses. RESULTS: Serum levels of IL-6 were significantly elevated in patients with clinically evident hormone refractory disease (5.7 +/- 1.9 pg/ml) and statistical significance was seen when comparing the elevated serum IL-6 levels to those in normal controls, prostatitis, BPH, and localized and ***recurrent*** disease, (P values < 0.01). Compared to serum levels of controls and BPH, PSA was significantly elevated in advanced untreated disease and hormone refractory groups (P < 0.05). Percent fPSA was significantly lower in all cancer patients but the hormone refractory. Serum ***PSMA*** was elevated in advanced untreated ***prostate*** ***cancer*** . Serum IL-6 showed positive correlation with PSMA and negative correlation with serum PSA but did not attain statistical significance. CONCLUSIONS: Serum IL-6 levels are significantly elevated in hormone-refractory prostate cancer patients and may be a surrogate marker of the androgen independent phenotype. Copyright 1999 Wiley-Liss, Inc.

Circulating levels of interleukin-6 in patients with hormone refractory ***prostate*** ***cancer*** .

... ***1999*** ,

... is found in high levels in human ejaculate, and has recently been found to regulate prostate-specific protein expression in prostate cancer cells through nonsteroidal activation of the androgen receptor. IL-6 may be a candidate mediator...

... IL-6 levels as a marker of disease progression. MATERIALS AND METHODS

Serum IL-6, prostate specific antigen (PSA), percent free PSA (%fPSA), and prostate-specific membrane antigen (PSMA) were measured using commercially available assays in 407 men, including 15 controls. The rest of the study population had clinical or histologic evidence of prostate diseases, including 41 patients with chronic prostatitis, 167 with benign prostatic hyperplasia (BPH), 8 with high-grade prostatic intraepithelial neoplasia (PIN), 88 with localized prostate cancer, 22 with local recurrence after treatment of primary tumor, 4 with advanced untreated disease (nodal or bony metastases), 23...

...while on hormone treatment and/or evidence of disease progression). None had history of concurrent ***malignancy*** or acute inflammatory condition. Kruskal-Wallis analysis of variance and Spearman's correlation analysis were...

... elevated serum IL-6 levels to those in normal controls, prostatitis, BPH, and localized and ***recurrent*** disease, (P values < 0.01). Compared to serum levels of controls and BPH, PSA was...

... disease and hormone refractory groups (P < 0.05). Percent fPSA was significantly lower in all cancer patients but the hormone refractory. Serum ***PSMA*** was elevated in advanced untreated ***prostate*** ***cancer*** . Serum IL-6 showed positive correlation with PSMA and negative correlation with serum PSA but did not attain statistical significance. CONCLUSIONS: Serum IL-6 levels are significantly elevated in hormone-refractory prostate cancer patients and may be a surrogate marker of the androgen independent phenotype. Copyright 1999 Wiley...

Descriptors: *Interleukin-6--blood--BL; *Neoplasm Recurrence, Local ; *Prostatic Neoplasms--physiopathology--PP; *Tumor Markers, Biological --analysis--AN...; Antineoplastic Agents, Hormonal--therapeutic use--TU; Disease Progression; Humans; Interleukin-6--pharmacology--PD; Middle Aged; Predictive Value of Tests; Prognosis; Prostate-Specific Antigen --blood--BL; Prostatic Neoplasms--drug therapy--DT; Research Support, Non-U.S. Gov...

Enzyme No.: EC 3.4.21.77 (***Prostate*** -Specific Antigen)

Chemical Name: Antineoplastic Agents, Hormonal; Interleukin-6; Tumor Markers, Biological; Prostate-Specific Antigen

11/3,K,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12530102 PMID: 10473985

Detection of prostate-specific antigen- or prostate-specific membrane antigen-positive circulating cells in prostatic ***cancer*** patients: clinical implications.

Millon R; Jacqmin D; Muller D; Guillot J; Eber M; Abecassis J

Laboratoire de Biologie Tumorale, Centre Paul Strauss, Hopitaux Universitaires, Strasbourg, France. btumorale@strasbourg.fnclcc.fr

European urology (SWITZERLAND) Oct 1999, 36 (4) p278-85, ISSN 0302-2838--Print Journal Code: 7512719

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

OBJECTIVES: To evaluate the clinical benefit from using circulating prostate-specific antigen (PSA) and prostate-specific membrane antigen (PSM) mRNA detection in prostate ***cancer*** staging and in follow-up. METHODS: Nested reverse

transcriptase-polymerase chain reaction (RT-PCR) assays were performed on RNA extracted from blood drawn from 56 patients with prostate ***cancer*** before any treatment. Additionally, assays were done on posttreatment samples from 50 patients who were followed up by serum PSA level, to determine whether any relationship exists between RT-PCR results and tumor ***recurrence*** . The ***prostate*** cell specificity of assays was evaluated by analysis of 21 blood samples from women or cystoprostatectomized men. RESULTS: With PSM RT-PCR assay, good sensitivity and prostate cell specificity could not be attained together, since high PSM mRNA illegitimate expression has been shown in some healthy donor bloods. For this reason, only PSA RT-PCR assay was used as a clinical marker. PSA mRNA was detected in peripheral blood of 4 out of 31 patients with clinically localized ***prostate*** ***cancer*** . It showed no relationship to the pathologic stage, but significant relationship to metastatic status, lymph node involvement and Gleason score. During follow-up, circulating PSA mRNA was detected in 8 out of 17 (47%) patients in treatment failure and in only 1 out of 33 (3%) successfully treated patients, with significant relationship between RT-PCR results and concomitant serum PSA levels. CONCLUSION: Our study reveals no significant advantage to PSA RT-PCR assay (1) in improving the staging of clinically localized prostate cancer or (2) in follow-up treatment failure, as compared to the usual ***recurrence*** marker (serum PSA). Additional investigations are needed to determine the ultimate significance and the management of patients with positive PSA RT-PCR assays.

Detection of prostate-specific antigen- or prostate-specific membrane antigen-positive circulating cells in prostatic ***cancer*** patients: clinical implications.

... ***1999*** ,

OBJECTIVES: To evaluate the clinical benefit from using circulating prostate-specific antigen (PSA) and prostate-specific membrane antigen (PSM) mRNA detection in prostate ***cancer*** staging and in follow-up. METHODS: Nested reverse transcriptase-polymerase chain reaction (RT-PCR) assays were performed on RNA extracted from blood drawn from 56 patients with prostate ***cancer*** before any treatment. Additionally, assays were done on posttreatment samples from 50 patients who were...

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... mRNA was detected in peripheral blood of 4 out of 31 patients with clinically localized ***prostate*** ***cancer*** . It showed no relationship to the pathologic stage, but significant relationship to metastatic status, lymph...

... significant advantage to PSA RT-PCR assay (1) in improving the staging of clinically localized prostate cancer or (2) in follow-up treatment failure, as compared to the usual recurrence marker (serum PSA). Additional investigations are needed to determine the ultimate significance and the management...

Descriptors: *Antigens, Surface; *Carboxypeptidases--blood--BL; *Neoplasm Circulating Cells; *Prostate-Specific Antigen--blood--BL; *Prostatic Neoplasms--blood--BL; *Prostatic Neoplasms--diagnosis--DI...; Neoplasm --blood--BL; Evaluation Studies; Glutamate Carboxypeptidase II; Humans; Lymphatic Metastasis--diagnosis--DI; Neoplasm Staging; Predictive Value of Tests; Prospective Studies; Research Support, Non-U.S. Gov't; Reverse Transcriptase Polymerase...

...Enzyme No.: II); EC 3.4.17.21 (glutamate carboxypeptidase II, human) ; EC 3.4.21.77 (***Prostate*** -Specific Antigen)

Chemical Name: Antigens, Neoplasm; Antigens, Surface; Tumor Markers, Biological; Carboxypeptidases; Glutamate Carboxypeptidase II; glutamate carboxypeptidase II, human; Prostate-Specific Antigen

11/3,K,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12499364 PMID: 10444137

Preoperative nested reverse transcription-polymerase chain reaction for prostate specific membrane antigen predicts biochemical ***recurrence*** after radical prostatectomy.

Okegawa T; Nutahara K; Higashihara E

Department of Urology, Kyorin University School of Medicine, Mitaka, Tokyo, Japan.

BJU international (ENGLAND) Jul 1999, 84 (1) p112-7, ISSN 1464-4096--Print Journal Code: 100886721

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

OBJECTIVE: To assess the utility of the nested reverse transcription-polymerase chain reaction (RT-PCR) method for measuring prostate specific membrane antigen (PSM) and prostate specific antigen (PSA) in predicting serum PSA ***recurrence*** after radical prostatectomy. PATIENTS AND METHODS: Nested RT-PCRs for PSM and PSA were used in 40 patients who subsequently underwent radical prostatectomy. The accuracy of the RT-PCR assays in predicting PSA failure was compared with those for the preoperative serum PSA level, Gleason score and final pathological staging. The patients were monitored using a PSA assay (Tandem-R, Hybritech, San Diego, CA) at 3 weeks after radical prostatectomy and every 2 months thereafter. Biochemical ***recurrence*** was defined as a serum PSA level of >/=0.4 ng/mL. RESULTS: Statistical analysis indicated that the nested RT-PCR assay for PSM was the most accurate preoperative predictor of potential surgical failure (PCR-PSM, P<0.001; PCR-PSA, P=0.018; serum PSA level, P=0.149; Gleason score P=0.388, by Fisher's exact probability test). Biochemical recurrence was evaluated in relation to these methods during a mean (range) follow-up of 16.7 (6-35) months. Of the 40 patients, eight (20%, one with organ-confined cancer and seven with extraprostatic extension of cancer) developed biochemical ***recurrence*** . The Kaplan-Meier ***recurrence*** -free actuarial probability curves differed significantly between patients with positive and those with negative results for the preoperative nested RT-PCR for PSM (P<0.01, generalized Wilcoxon's test). The nested RT-PCR for PSA, preoperative serum PSA value and Gleason score were not significant ***predictors*** of biochemical ***recurrence*** (P=0.16, 0.12 and 0.24, respectively). CONCLUSIONS: The nested RT-PCR for PSM was the best preoperative predictor of biochemical recurrence among the factors examined.

Preoperative nested reverse transcription-polymerase chain reaction for prostate specific membrane antigen predicts biochemical ***recurrence*** after radical prostatectomy.

... ***1999*** ,

... the utility of the nested reverse transcription-polymerase chain reaction (RT-PCR) method for measuring prostate specific membrane antigen (PSM) and prostate specific antigen (PSA) in predicting serum PSA recurrence after radical prostatectomy. PATIENTS AND METHODS: Nested RT-PCRs for PSM and PSA were used...

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...San Diego, CA) at 3 weeks after radical prostatectomy and every 2 months thereafter. Biochemical ***recurrence*** was defined as a serum PSA level of >/=0.4 ng/mL. RESULTS: Statistical analysis indicated that the nested RT-PCR assay for PSM was the most accurate preoperative predictor of potential surgical failure (PCR-PSM, P<0.001; PCR-PSA, P=0.018; serum...

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Descriptors: *Neoplasm Recurrence, Local--blood--BL; * Prostate-Specific Antigen--blood--BL; *Prostatic Neoplasms--blood--BL ; *Reverse Transcriptase Polymerase Chain Reaction; Aged; Humans; Middle Aged; Predictive Value of Tests; Prognosis; Prostatectomy; Prostatic Neoplasms--surgery--SU; Research Support, Non-U.S. Gov

Enzyme No.: EC 3.4.21.77 (***Prostate*** -Specific Antigen)

Chemical Name: Prostate-Specific Antigen

11/3,K,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11/07

12204450 PMID: 10632336

Prostate-specific membrane antigen levels in sera from healthy men and patients with benign prostate hyperplasia or ***prostate*** ***cancer*** .

Beckett M L; Cazares L H; Vlahou A; Schellhammer P F; Wright G L

Department of Microbiology and Molecular Cell Biology, Virginia Prostate Center, Eastern Virginia Medical School, Norfolk 23501, USA.

Clinical cancer research - an official journal of the American Association for Cancer Research (UNITED STATES) Dec 1999, 5 (12) p4034-40, ISSN 1078-0432--Print Journal Code: 9502500

Contract/Grant No.: CA 26659; CA; NCI; DK47754; DK; NIDDK

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Prostate-specific membrane antigen (PSMA) serum levels have been proposed to be of prognostic significance in patients with advanced ***prostate*** disease. The objective of the present study was to confirm PSMA serum expression by Western blot techniques, to determine whether such data could assist in the differentiation of benign from malignant prostatic disease, and to determine the suitability of serum PSMA measurements in predicting recurrent or progressive prostate ***malignancies*** . We measured ***PSMA*** , a transmembrane glycoprotein identified in prostate epithelial cells, in the sera of 236 normal

individuals and ***cancer*** patients by Western blot analysis. Within the normal male population, PSMA levels increase with age and were found to be significantly elevated in subjects more than 50 years of age when compared to those of younger men. We did not confirm previous reports that serum PSMA measurements could distinguish late-stage prostate carcinoma from early-stage prostate carcinoma, nor did we find PSMA to be more effective than prostate-specific antigen in monitoring ***prostate*** ***cancer*** patient prognosis. Furthermore, we found elevated serum PSMA in healthy females, and, similar to the healthy male population, the levels increased with age, with the highest levels found in the sera from breast ***cancer*** patients. These latter observations further support that PSMA is not a specific biomarker for prostate cancer and that a variety of normal and diseased tissue may contribute to the serum levels of ***PSMA*** .

Prostate-specific membrane antigen levels in sera from healthy men and patients with benign prostate hyperplasia or ***prostate*** ***cancer*** .
... ***1999*** ,
Prostate-specific membrane antigen (PSMA) serum levels have been proposed to be of prognostic significance in patients with advanced ***prostate*** disease. The objective of the present study was to confirm PSMA serum expression by Western blot techniques, to determine whether such data could assist in the differentiation of benign from malignant prostatic disease, and to determine the suitability of serum PSMA measurements in predicting recurrent or progressive prostate ***malignancies*** . We measured ***PSMA*** , a transmembrane glycoprotein identified in prostate epithelial cells, in the sera of 236 normal individuals and ***cancer*** patients by Western blot analysis. Within the normal male population, PSMA levels increase with age and were found to be significantly elevated in subjects more than...

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; Adult; Aged; Aged, 80 and over; Comparative Study; Glutamate Carboxypeptidase II; Humans; Middle Aged; Prostate-Specific Antigen --blood--BL; Prostatic Hyperplasia--diagnosis--DI; Prostatic Neoplasms --diagnosis--DI; Prostatic Neoplasms--pathology...
...Enzyme No.: II); EC 3.4.17.21 (glutamate carboxypeptidase II, human) ; EC 3.4.21.77 (***Prostate*** -Specific Antigen)
Chemical Name: Antigens, Neoplasm; Antigens, Surface; Carboxypeptidases; Glutamate Carboxypeptidase II; glutamate carboxypeptidase II, human; Prostate-Specific Antigen

11/3,K,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11958620 PMID: 9790041
Indium-111 capromab pendetide (ProstaScint) imaging to detect ***recurrent*** and metastatic ***prostate*** ***cancer*** .

Petronis J D; Regan F; Lin K
Department of Radiology, Johns Hopkins Bayview Medical Center, Johns Hopkins Medical Institutions, Baltimore, Maryland 21224-2780, USA.
Clinical nuclear medicine (UNITED STATES) Oct 1998, 23 (10) p672-7, ISSN 0363-9762--Print Journal Code: 7611109
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
This study evaluated the utility of In-111 capromab pendetide imaging to detect ***prostate*** ***cancer*** metastases or local ***recurrence*** .
The specific goal was to identify clinical factors such as prostate -specific antigen, pathologic stage, and Gleason score that were most ***predictive*** of a positive scan outcome. In addition, a new concept of a weighted Gleason score was defined and correlated with the scan outcome. Fifty-one patients with an elevated prostate-specific antigen level and otherwise negative workup were studied. Forty-eight patients had been treated by radical prostatectomy, two by radiation therapy, and one patient was studied before prostatectomy. Each patient received an intravenous injection of approximately 5 mCi of In-111 containing 0.5 mg of CYT 356, a conjugated site-specific monoclonal antibody against prostate ***specific*** ***membrane*** ***antigen*** . Tomographic blood pool images
were obtained the day of injection. Four days later planar images and tomographic images of the abdomen and pelvis were obtained. Scans were interpreted by two experienced nuclear medicine physicians. Differences in the scan interpretation were settled by consensus. Scan outcomes were correlated with prostate-specific antigen levels, pathologic stage, Gleason score, weighted Gleason score, and clinical data. Of 51 scans, 70.6% (36 of 51) were positive. Eight patients had abnormal activity in the prostatic fossa, 12 patients had abnormal activity in the abdominal or pelvic lymph nodes, and 16 patients demonstrated abnormal activity in both areas. One patient with a positive scan underwent lymphadenectomy and was confirmed to be a true positive. Patients with a ***prostate*** -specific antigen level greater than 10 ng/ml, a weighted Gleason score higher than 4.5, or ***prostate*** -specific antigen levels greater than 2 ng/ml plus a weighted score higher than 4.5 showed positive rates of 100% (6 of 6), 88.2% (14 of 16), and 100% (6 of 6), respectively. In-111 capromab pendetide imaging was useful to detect metastases or local recurrence . Serum ***prostate*** -specific antigen levels and weighted Gleason scores are good predictive factors of the likelihood of a positive scan outcome.

Indium-111 capromab pendetide (ProstaScint) imaging to detect ***recurrent*** and metastatic ***prostate*** ***cancer*** . ... ***1998*** ,

This study evaluated the utility of In-111 capromab pendetide imaging to detect ***prostate*** ***cancer*** metastases or local ***recurrence*** .
The specific goal was to identify clinical factors such as prostate -specific antigen, pathologic stage, and Gleason score that were most ***predictive*** of a positive scan outcome. In addition, a new concept of a weighted Gleason score was defined and correlated with the scan outcome. Fifty-one patients with an elevated prostate-specific antigen level and otherwise negative workup were studied. Forty-eight patients had been treated...

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... positive scan underwent lymphadenectomy and was confirmed to be a true positive. Patients with a ***prostate*** -specific antigen level greater than 10 ng/ml, a weighted Gleason score higher than 4.5, or ***prostate*** -specific antigen levels greater than 2 ng/ml plus a weighted score higher than 4...

... of 6), respectively. In-111 capromab pendetide imaging was useful to detect metastases or local ***recurrence*** . Serum ***prostate*** -specific antigen levels and weighted Gleason scores are good predictive factors of the likelihood of a positive scan outcome.

...Descriptors: Abdominal Neoplasms--secondary--SC; *Antibodies, Monoclonal--diagnostic use--DU; *Indium Radioisotopes--diagnostic use--DU; *Neoplasm Recurrence, Local--radionuclide imaging--RI; *Prostatic Neoplasms--radionuclide imaging--RI; *Radioimmunodetection; Humans; Prostate-Specific Antigen--analysis--AN; Prostatic Neoplasms --diagnosis--DI; Prostatic Neoplasms--pathology--PA; Prostatic Neoplasms --surgery...

Enzyme No.: EC 3.4.21.77 (***Prostate*** -Specific Antigen)

Chemical Name: Antibodies, Monoclonal; Indium Radioisotopes; Capromab Pendetide; Prostate-Specific Antigen

11/3,K,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11788103 PMID: 9610707

Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases.

Bostwick D G; Pacelli A; Blute M; Roche P; Murphy G P

Department of Laboratory Medicine and Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905, USA.

Cancer (UNITED STATES) Jun 1 1998, 82 (11) p2256-61, ISSN 0008-543X--Print Journal Code: 0374236

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

BACKGROUND: Prostate specific membrane antigen (PSM) is a membrane-bound antigen that is highly specific for benign and ***malignant*** ***prostate*** epithelial cells. Its expression in high grade prostatic intraepithelial neoplasia (PIN) has not been compared with that in ***prostate*** ***carcinoma*** . METHODS: The authors performed an immunohistochemical study of representative sections from 184 radical prostatectomies from previously untreated patients with pathologic stage T2N0M0 adenocarcinoma treated at the Mayo Clinic between 1987 and 1991. Affinity-purified monoclonal antibody 7E11-5.3 directed against PSM was employed at a concentration of 20 microg/mL overnight. For comparison, serial sections in each case were stained with prostate specific antigen (PSA). Staining for all antibodies was performed using the streptavidin-biotin method. For each case, the percentage of immunoreactive cells in benign epithelium, PIN, and adenocarcinoma was estimated in increments of 10%. Cox proportional hazards models were used to identify the risk of carcinoma recurrence according to the number of immunoreactive PIN or cancer cells for PSM and PSA; the date of

radical prostatectomy was used as the starting time, and serum PSA (biochemical) failure or clinical failure was the event. PSA biochemical failure was defined as serum PSA > 0.2 ng/mL at least 30 days after surgery. RESULTS: Intense cytoplasmic immunoreactivity for PSM was observed in the benign and neoplastic epithelial cells in all cases (100% of cases staining). The number of cells staining was lower in benign epithelium and PIN than in adenocarcinoma (69.5+/-17.3% [range, 20-90%] vs. 77.9+/-13.2% [range, 30-100%] vs. 80.2+/-13.7% [range, 30-100%], respectively). With rare exceptions, basal cells were negative, and there was no immunoreactivity of the ***prostate*** stroma, urothelium, or vasculature. Adenocarcinoma gave the most intense and extensive staining, and the highest grades of adenocarcinoma (Gleason primary patterns 4 and 5) showed staining in virtually every cell; there was greater heterogeneity of staining in lower grades of adenocarcinoma. By contrast, PSA immunoreactivity was more intense and extensive in benign epithelium than in PIN and adenocarcinoma. The number of immunoreactive PIN or ***cancer*** cells for PSM and PSA was not predictive of PSA biochemical or clinical failure as defined in this study. CONCLUSIONS: PSM was expressed in all cases of prostate adenocarcinoma, with the greatest extent and intensity observed in the highest grades. The expression increased incrementally from benign epithelium to high grade PIN or adenocarcinoma. Conversely, PSA showed the greatest staining in benign epithelium, with decreased expression incrementally from benign epithelium to high grade PIN or adenocarcinoma. Expression of PSM is clinically useful for the identification of prostate epithelium, particularly PIN or adenocarcinoma, and its expression is regulated independent of PSA. The number of PSM immunoreactive cells was not predictive of recurrence , most likely because of the presence of abundant immunoreactivity in most cases, or because of differential expression in primary and metastatic disease.

Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases.

... ***1998*** ,

BACKGROUND: Prostate specific membrane antigen (PSM) is a membrane-bound antigen that is highly specific for benign and ***malignant*** ***prostate*** epithelial cells. Its expression in high grade prostatic intraepithelial neoplasia (PIN) has not been compared with that in ***prostate*** ***carcinoma*** . METHODS: The authors performed an immunohistochemical study of representative sections from 184 radical prostatectomies from...

... of 20 microg/mL overnight. For comparison, serial sections in each case were stained with ***prostate*** specific antigen (PSA). Staining for all antibodies was performed using the streptavidin-biotin method. For...

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...; pathology--PA; Adult; Aged; Aged, 80 and over; Glutamate Carboxypeptidase II; Humans; Immunohistochemistry; Middle Aged; Prostate-Specific Antigen--analysis--AN; Prostatic Intraepithelial Neoplasia--pathology--PA; Prostatic Neoplasms--pathology--PA
...Enzyme No.: II); EC 3.4.17.21 (glutamate carboxypeptidase II, human) ; EC 3.4.21.77 (***Prostate*** -Specific Antigen)
Chemical Name: Antigens, Surface; Carboxypeptidases; Glutamate Carboxypeptidase II; glutamate carboxypeptidase II, human; Prostate -Specific Antigen

11/3,K,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11754989 PMID: 9571393
Capromab pendetide. A review of its use as an imaging agent in ***prostate*** ***cancer*** .
Lamb H M; Faulds D
Adis International Limited, Auckland, New Zealand. demail@adis.co.nz
Drugs & aging (NEW ZEALAND) Apr 1998, 12 (4) p293-304, ISSN 1170-229X--Print Journal Code: 9102074
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Capromab pendetide, radiolabelled with indium-111, is a radioimmunoscintigraphic imaging agent used in patients with prostate ***cancer*** . It consists of a murine monoclonal antibody (7E11-C5.3) covalently jointed to a linker-chelator molecule. 7E11-C5.3 is thought to be directed against the intracellular domain of human prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein expressed by ***prostate*** epithelial cells. The diagnostic utility of capromab pendetide has been investigated in 2 distinct patient groups. In patients with untreated ***prostate*** ***cancer*** at high risk for pelvic lymph node metastases, capromab pendetide imaging had respective sensitivities and specificities of 52 and 96% in 1 study and 62 and 72% in another, as confirmed by pelvic lymph node dissection biopsy results. In patients with suspected occult ***recurrent*** or residual disease after prostatectomy, capromab pendetide had respective sensitivities and specificities of 49 and 71% in 1 study and 77 and 35% in another for detection of ***cancer*** in the ***prostate*** bed. Almost half of these patients also had evidence of lesions outside the prostate fossa (usually in the pelvic and abdominal lymph nodes) according to immunoscintigraphic scans, but too few cases were confirmed to allow an evaluation of capromab pendetide. Four per cent of patients who received single doses of capromab pendetide experienced adverse events. Elevated bilirubin levels, hypertension and hypotension each affected 1% of patients and elevated liver enzymes and injection site reactions < 1% of patients. Detectable human anti-mouse antibodies were reported in 8% of patients after a single dose of capromab pendetide and in 19% of patients after repeat infusions. CONCLUSIONS: Capromab pendetide offers improved sensitivity in the detection of prostate cancer over other noninvasive techniques. When used in conjunction with other techniques, it offers the possibility of defining the extent of localised and metastatic disease, thereby refining patient management.

Capromab pendetide. A review of its use as an imaging agent in ***prostate*** ***cancer*** .
... ***1998*** ,
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11/3,K,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11500015 PMID: 9337346
Prospective analysis of prostate-specific markers in pelvic lymph nodes of patients with high- ***risk*** ***prostate*** ***cancer*** .
Ferrari A C; Stone N N; Eyler J N; Gao M; Mandeli J; Unger P; Gallagher R E; Stock R
Division of Neoplastic Diseases, Mount Sinai School of Medicine, New York, NY 10029, USA.
Journal of the National Cancer Institute (UNITED STATES) Oct 15 1997, 89 (20) p1498-504, ISSN 0027-8874--Print Journal Code: 7503089
Publishing Model Print; Comment in J Natl Cancer Inst. 1997 Oct 15;89(20) 1471-3; Comment in PMID 9337337
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND: Pathologic evidence of pelvic lymph node involvement is obtained in 12%-20% of patients with localized prostate cancer that exhibits high-risk features (defined on the basis of tumor size, serum ***prostate*** -specific antigen [PSA] level, or Gleason score). The rate of systemic failure (i.e., ***relapse***) in patients with this type of prostate cancer and no pathologic evidence of regional lymph node involvement is 55%-92% within 5 years of definitive local therapy. Since reverse transcription-polymerase chain reaction (RT-PCR) methods are likely to be more sensitive than routine pathologic examination in detecting metastatic tumor cells, we compared the ability of the two approaches to detect prostate cells in the pelvic lymph nodes of

patients with localized, high- ***risk*** disease. METHODS: Fifty-eight lymph node specimens isolated from 33 patients before definitive local therapy were examined. Expression of PSA and ***prostate*** - ***specific*** membrane antigen (PSM) messenger RNAs in the specimens was assessed by means of nested RT-PCR. RESULTS: Pathologic examination identified tumor cells in the lymph nodes of four (12%) of the 33 patients, and PSA and/ or PSM expression was positive in specimens from 27 (82%) of the patients (two-sided P<.0001). The four patients with positive pathologic findings also had positive RT-PCR results. Among the 29 patients with no pathologic evidence of lymph node involvement, 23 (79%) tested positive by means of RT-PCR. In these 23 patients, PSM expression was detected more frequently than PSA expression; however, in two patients, only PSA expression was detected. CONCLUSIONS: Expression of ***prostate*** -specific markers in the pelvic lymph nodes of patients with localized, high-risk prostate cancer may indicate the presence of metastatic tumor cells. Such cells may be responsible for the high rate of systemic failure seen in these patients. Additional studies are required to determine the prognostic relevance of our findings.

Prospective analysis of prostate-specific markers in pelvic lymph nodes of patients with high- ***risk*** ***prostate*** ***cancer*** ... ***1997*** ,

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...Descriptors: Neoplasm--analysis--AN; *Antigens, Surface--analysis--AN; *Lymph Nodes--pathology--PA; *Lymphatic Metastasis--pathology--PA; *Prostate-Specific Antigen--analysis--AN; *Prostatic Neoplasms --pathology--PA; *Tumor Markers, Biological--analysis--AN...; Antigens, Surface--biosynthesis--BI; Comparative Study; Glutamate Carboxypeptidase II ; Humans; Neoplasm Staging; Polymerase Chain Reaction; Predictive Value of Tests; Prospective Studies; Prostate-Specific Antigen --biosynthesis--BI; Reproducibility of Results; Research Support, Non-U.S. Gov't; Risk Factors; Sensitivity and Specificity

...Enzyme No.: II); EC 3.4.17.21 (glutamate carboxypeptidase II, human) ; EC 3.4.21.77 (***Prostate*** -Specific Antigen)

Chemical Name: Antigens, Neoplasm; Antigens, Surface; Tumor Markers, Biological; Glutamate Carboxypeptidase II; glutamate carboxypeptidase II, human; Prostate-Specific Antigen

11/3,K,AB/17 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

0013218303 BIOSIS NO.: 200100390142

A positive preoperative PSMA RT-PCR assay in blood predicts
biological recurrence after radical prostatectomy
AUTHOR: Eschwege Pascal (Reprint); Droupy Stephabe (Reprint); Loric Sylvain (Reprint); Blanchet Pascal (Reprint); Paradis Valerie (Reprint); Hammoudi Yacine (Reprint); Izard Vincent (Reprint); Jardin Alain (Reprint); Benoit Gerard (Reprint)
AUTHOR ADDRESS: Bicetre Hospital, AP-HP, Le Kremlin Bicetre, France**France
JOURNAL: European Urology 39 (Suppl. 5): p149 March, 2001 ***2001***
MEDIUM: print
CONFERENCE/MEETING: XVIth Congress of the European Association of Urology Geneva, Switzerland April 07-10, 2001; 20010407
SPONSOR: European Association of Urology
ISSN: 0302-2838
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

A positive preoperative PSMA RT-PCR assay in blood predicts
biological recurrence after radical prostatectomy
2001
DESCRIPTORS:
...ORGANISMS: PARTS ETC: ***prostate*** --
DISEASES: prostate cancer--
CHEMICALS & BIOCHEMICALS: PSA { ***prostate*** specific antigen...

... ***PSMA*** mRNA { ***PSMA*** messenger RNA
...METHODS & EQUIPMENT: ***PSMA*** RT-PCR assay { ***PSMA*** reverse transcriptase-polymerase chain reaction assay
MISCELLANEOUS TERMS: biological ***recurrence*** probability...

11/3,K,AB/18 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

11084676 Genuine Article#: 603YM Number of References: 23
Title: The role of In-111 Capromab Pendetide (ProstaScint(R)) immunoscintigraphy in the management of prostate cancer (ABSTRACT AVAILABLE)
Author(s): Freeman LM (REPRINT) ; Krynyckyi BR; Li Y; Korupulu G; Saleemi K ; Haseman MK; Kahn D
Corporate Author(s): Natl ProstascintR Study Grp
Corporate Source: Montefiore Med Ctr,Dept Nucl Med,111 E 210th St/Bronx//NY/10467 (REPRINT); Montefiore Med Ctr,Dept Nucl Med,Bronx//NY/10467; Albert Einstein Coll Med,Bronx//NY/10467; Sutter Community Hosp,Sacramento//CA/; Vet Adm Med Ctr,Iowa City//IA/
Journal: QUARTERLY JOURNAL OF NUCLEAR MEDICINE, 2002, V46, N2 (JUN) , P131-137
ISSN: 1125-0135 Publication date: 20020600
Publisher: EDIZIONI MINERVA MEDICA, CORSO BRAMANTE 83-85 INT JOURNALS DEPT., 10126 TURIN, ITALY
Language: English Document Type: REVIEW
Abstract: In-111 Capromab Pendetide (ProstaScint(R)) is a whole murine antibody that is reactive with prostate specific membrane antigen (PSMA), a glycoprotein on the surface of normal and abnormal ***prostate*** epithelium. it has proven to be of great value in assisting management decisions in prostate cancer patients who initially present with high risk for metastatic spread, or who develop a picture of ***recurrent*** disease after surgery or radiation therapy. Patterns of metastatic lymphatic spread have correlated well with autopsy reports in the literature. Unfortunately, other imaging study and/or histologic confirmation of scintigraphic findings has been difficult to obtain.

Prostascint's role in predicting durable complete response (DCR) in postoperative patients having salvage radiotherapy to their ***prostate*** fossa is very promising. Further investigative work in larger patient Populations is needed to confirm these early results.

Title: The role of In-111 Capromab Pendetide (ProstaScint(R)) immunoscintigraphy in the management of prostate cancer
, 2002
Abstract: In-111 Capromab Pendetide (ProstaScint(R)) is a whole murine antibody that is reactive with prostate specific membrane antigen (PSMA), a glycoprotein on the surface of normal and abnormal ***prostate*** epithelium. it has proven to be of great value in assisting management decisions in prostate cancer patients who initially present with high risk for metastatic spread, or who develop a picture of ***recurrent*** disease after surgery or radiation therapy. Patterns of metastatic lymphatic spread have correlated well with...

...or histologic confirmation of scintigraphic findings has been difficult to obtain. Prostascint's role in ***predicting*** durable complete response (DCR) in postoperative patients having salvage radiotherapy to their ***prostate*** fossa is very promising. Further investigative work in larger patient Populations is needed to confirm...
...Identifiers--111)INDIUM-CAPROMAB PENDETIDE; RADICAL PROSTATECTOMY; METASTATIC PATTERNS; MEMBRANE ANTIGEN; THERAPY; CARCINOMA

11/3,K,AB/19 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07354734 Genuine Article#: 154NV Number of References: 9
Title: Neither PSMA RT-PCR nor MTHFR genotype predicts PSA failure after prostatectomy (ABSTRACT AVAILABLE)
Author(s): Kaplinsky RS; Bacich DJ; OKeefe DS; Rabbani F; Tomassi MJ; Huryk R; Baster AL; Miller WH; Heston WDW (REPRINT) ; Fair WR
Corporate Source: MEM SLOAN KETTERING CANC CTR,MOL PHARMACOL & THERAPEUT SECT, UROL ONCOL RES LAB, 1275 YORK AVE/NEW YORK//NY/10021 (REPRINT); MEM SLOAN KETTERING CANC CTR,MOL PHARMACOL & THERAPEUT SECT, UROL ONCOL RES LAB/NEW YORK//NY/10021; MEM SLOAN KETTERING CANC CTR,UROL SERV/NEW YORK//NY/10021
Journal: MOLECULAR UROLOGY, 1998, V2, N3 (FAL), P221-225
ISSN: 1091-5362 Publication date: 19980900
Publisher: MARY ANN LIEBERT INC PUBL, 2 MADISON AVENUE, LARCHMONT, NY 10538
Language: English Document Type: ARTICLE
Abstract: Previously, we reported that about 50% of prostate cancer patients had circulating tumor cells prior to radical prostatectomy regardless of whether they were subsequently found to have stage pT(2) or pT(3) disease, We also observed that after neoadjuvant hormone deprivation prior to prostatectomy, only 27% of patients expressed prostate specific membrane antigen (PSMA) by reverse transcriptase-polymerase chain reaction (RT-PCR), indicating that neoadjuvant hormone deprivation decreased the number of patients positive for circulating cells, With a median follow-up of 2 years, we have examined whether the presence of circulating cells detected by RT-PCR for PSMA was predictive of subsequent failure, as judged by prostate specific antigen (PSA), after radical prostatectomy and found that it was not. We had identified ***PSMA*** as a unique folate hydrolase and thus can potentially subject cells to folate deficiency. We questioned whether the presence of a thermolabile methylenetetrahydrofolate reductase (MTHFR) may identify a group of patients whose cancers would have a more aggressive phenotype, We did not find that patients

with the thermolabile MTHFR phenotype were more likely to have disease recurrence after radical prostatectomy, Thus, better markers of malignant potential are required to identify those patients with prostate cancer who are destined to have a recurrence after prostatectomy.

Title: Neither PSMA RT-PCR nor MTHFR genotype predicts PSA failure after prostatectomy
, 1998
Abstract: Previously, we reported that about 50% of prostate cancer patients had circulating tumor cells prior to radical prostatectomy regardless of whether they were subsequently...

...also observed that after neoadjuvant hormone deprivation prior to prostatectomy, only 27% of patients expressed prostate specific membrane antigen (PSMA) by reverse transcriptase-polymerase chain reaction (RT-PCR), indicating that neoadjuvant hormone deprivation decreased the...

...years, we have examined whether the presence of circulating cells detected by RT-PCR for PSMA was predictive of subsequent failure, as judged by prostate specific antigen (PSA), after radical prostatectomy and found that it was not. We had identified PSMA as a unique folate hydrolase and thus can potentially subject cells to folate deficiency. We...

...the presence of a thermolabile methylenetetrahydrofolate reductase (MTHFR) may identify a group of patients whose cancers would have a more aggressive phenotype, We did not find that patients with the thermolabile MTHFR phenotype were more likely to have disease recurrence after radical prostatectomy, Thus, better markers of malignant potential are required to identify those patients with prostate cancer who are destined to have a recurrence after prostatectomy.
...Identifiers--MEMBRANE ANTIGEN; ***CANCER; *** CELLS
?

12/3,K,AB/36 (Item 2 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 3967710 IFI Acc No: 0041688
IFI Publication Control No: 0041688
Document Type: C
(A1) METHODS AND REAGENTS FOR THE RAPID AND EFFICIENT ISOLATION OF CIRCULATING CANCER CELLS; DETECTING PREFERENTIAL CELLS IN SAMPLE; OBTAIN SAMPLE, MIX WITH MAGNETIC PARTICLES, INCUBATE WITH LABEL, ANALYZE LABELED CELLS
(B2) METHODS AND REAGENTS FOR THE RAPID AND EFFICIENT ISOLATION OF CIRCULATING CANCER CELLS; DETECTING PREFERENTIAL CELLS IN SAMPLE; OBTAIN SAMPLE, MIX WITH MAGNETIC PARTICLES, INCUBATE WITH LABEL, ANALYZE LABELED CELLS
Inventors: Liberti Paul A (US); Racila Emilian V (US); Rao Galla Chandra (US); Terstappen Leon W M M (US); Uhr Jonathan W (US)
Assignee: (A1) Unassigned Or Assigned To Individual
(B2) Immunivest Corp
Assignee Code: (A1) 68000; (B2) 37402
Probable Assignee: Immunivest Corp
Attorney, Agent or Firm: Dann, Dorfman, Herrell and Skillman
Publication (No,Kind,Date), Applic (No,Date):
US 20020009759 A1 20020124 US 2001904472 20010713
US 6645731 B2 20031111 US 2001904472 20010713
Calculated Expiration: 20190212
Notes: INDEXED FROM APPLICATION
Prior Publication(No,Date),Applic(No,Date):US 20020009759 A1 20020124
Priority Applic(No,Date): US 2001904472 20010713; US 99248388

12/3,K,AB/32 (Item 11 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07822737 Genuine Article#: 212BL Number of References: 43
Title: Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature (ABSTRACT AVAILABLE)
Author(s): Chang SS; Reuter VE; Heston WDW; Bander NH; Grauer LS; Gaudin PB (REPRINT)
Corporate Source: MEM SLOAN KETTERING CANC CTR,DEPT PATHOL, 1275 YORK AVE/NEW YORK//NY/10021 (REPRINT); MEM SLOAN KETTERING CANC CTR,DEPT PATHOL/NEW YORK//NY/10021; GEORGE M OBRIEN UROL RES CTR,DEPT SURG, SERV UROL/NEW YORK//NY/10021; HYBRITECH INC,/SAN DIEGO//CA/92196; CORNELL UNIV,NEW YORK PRESBYTERIAN HOSP, DEPT UROL, WEILL MED COLL/NEW YORK//NY/10021; LUDWIG INST CANC RES,/NEW YORK//NY/10021
Journal: CANCER RESEARCH, 1999, V59, N13 (JUL 1), P3192-3198
ISSN: 0008-5472 Publication date: 19990701
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202
Language: English Document Type: ARTICLE
Abstract: Prostate-specific membrane antigen (PSMA) is a type II integral membrane glycoprotein that was initially characterized by the monoclonal antibody (mAb) 7E11. PSMA is highly expressed in prostate secretory-acinar epithelium and prostate cancer as well as in several extraprostatic tissues. Recent evidence suggests that ***PSMA*** is also expressed in tumor-associated neovasculature. We examined the immunohistochemical characteristics of 7E11 and those of four recently developed anti- ***PSMA*** mAbs (J591, J415, and Hybritech PEQ226.5 and PM2J004.5), each of which binds a distinct epitope of ***PSMA*** . Using the streptavidin-biotin method, we evaluated these mAbs in viable prostate cancer cell lines and various fresh-frozen benign and ***malignant*** tissue specimens. In the latter, we compared the localization of the anti-PSMA mAbs to that of the antiendothelial cell mAb CD34. With rare exceptions, all five anti- ***PSMA*** mAbs reacted strongly with the neovasculature of a wide spectrum of malignant neoplasms: conventional (clear cell) renal carcinoma (11 of 11 cases), transitional cell carcinoma of the urinary bladder (6 of 6 cases), testicular embryonal carcinoma (1 of 1 case), colonic adenocarcinoma (5 of 5 cases), neuroendocrine carcinoma (5 of 5 cases), glioblastoma multiforme (1 of 1 cases), malignant melanoma (5 of 5 cases), pancreatic duct carcinoma (4 of 4 cases), non-small cell lung carcinoma (5 of 5 cases), soft tissue sarcoma (5 of 6 cases), breast carcinoma (5 of 6 cases), and prostatic adenocarcinoma (2 of 12 cases). Localization of the anti- ***PSMA*** mAbs to tumor-associated neovasculature was confirmed by CD34 immunohistochemistry in sequential tissue sections. Normal vascular endothelium in non-cancer-bearing tissue was consistently ***PSMA*** negative. The anti- ***PSMA*** mAbs reacted with the neoplastic cells of prostatic adenocarcinoma (12 of 12 cases) but not with the neoplastic cells of any other tumor type, including those of benign and malignant vascular tumors (0 of 3 hemangiomas, 0 of 1 hemangioendothelioma, and 0 of 1 angiosarcoma). The mAbs to the extracellular ***PSMA*** domain (J591, J415, and Hybritech PEQ226.5) bound viable prostate cancer cells (LNCaP and PC3-PIP), whereas the mAbs to the intracellular domain (7E11 and Hybritech PM2J004.5) did not. All five anti- ***PSMA*** mAbs reacted with fresh-Frozen benign prostate secretory-acinar epithelium (28 of 28 cases), duodenal columnar (brush border) epithelium (11 of 11 cases), proximal renal tubular epithelium (5 of 5 cases), colonic ganglion cells (1 of 12 cases), and benign breast epithelium (8 of 8 cases). A subset of skeletal muscle cells was positive with 7E11 (7 of

7 cases) and negative with the other four anti- ***PSMA*** mAbs. PSMA was consistently expressed in the neovasculature of a wide variety of malignant neoplasms and may be an effective target for mAb-based antineovasculature therapy.

Title: Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature
, 1999
Abstract: Prostate-specific membrane antigen (PSMA) is a type II integral membrane glycoprotein that was initially characterized by the monoclonal antibody (mAb) 7E11. PSMA is highly expressed in prostate secretory-acinar epithelium and prostate cance

12/3,K,AB/31 (Item 10 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08130245 Genuine Article#: 249PV Number of References: 38
Title: Prostate-specific membrane antigen: Much more than a prostate cancer marker (ABSTRACT AVAILABLE)
Author(s): Chang SS; Gaudin PB; Reuter VE; OKeefe DS; Bacich DJ; Heston WDW (REPRINT)
Corporate Source: MEM SLOAN KETTERING CANC CTR,GEORGE M OBRIEN UROL RES CTR, 1275 YORK AVE/NEW YORK//NY/10021 (REPRINT); MEM SLOAN KETTERING CANC CTR,GEORGE M OBRIEN UROL RES CTR/NEW YORK//NY/10021; MEM SLOAN KETTERING CANC CTR,DEPT PATHOL/NEW YORK//NY/10021
Journal: MOLECULAR UROLOGY, 1999, V3, N3 (FAL), P313-319
ISSN: 1091-5362 Publication date: 19990900
Publisher: MARY ANN LIEBERT INC PUBL, 2 MADISON AVENUE, LARCHMONT, NY 10538
Language: English Document Type: ARTICLE
Abstract: Prostate cancer continues to be the most common cancer and second leading cause of cancer-related death among men. The use of markers, particularly serum-based ***prostate*** specific antigen (PSA), has contributed to the rapid rise in diagnosed cases in the late 1980s and early 1990s, but new diagnostic and possible therapeutic markers are needed and are currently being evaluated. One of these, ***prostate*** - ***specific*** ***membrane*** antigen (PSMA), is an approximately 100-kDa type II transmembrane protein originally thought to be highly selectively expressed in all types of prostatic tissue, with expression being upregulated in androgen-depleted or androgen-independent states. The radioimmunoconjugate form of the anti-PSMA monoclonal antibody (mAb) 7E11 is currently being used to diagnose prostate ***cancer*** metastasis and ***recurrence*** . In addition, Phase I and II trials have started utilizing PSMA in different therapeutic ways, with promising results. Recent exciting work has demonstrated PSMA expression in endothelial cells of vessels restricted to the tumor-associated neo-vasculature. This finding expands the possible beneficial uses of PSMA, as new anti-PSMA mAbs continue to be developed.

Title: Prostate-specific membrane antigen: Much more than a prostate cancer marker
, 1999
Abstract: Prostate cancer continues to be the most common cancer and second leading cause of cancer-related death among men. The use of markers, particularly serum-based ***prostate*** specific antigen (PSA), has contributed to the rapid rise in diagnosed cases in the late...
...diagnostic and possible therapeutic markers are needed and are currently being evaluated. One of these, ***prostate*** - ***specific*** membrane antigen (PSMA), is an approximately 100-kDa type II transmembrane protein originally thought to be highly selectively...

...being upregulated in androgen-depleted or androgen-independent states. The radioimmunoconjugate form of the anti-PSMA monoclonal antibody (mAb) 7E11 is currently being used to diagnose prostate ***cancer*** metastasis and ***recurrence*** . In addition, Phase I and II trials have started utilizing PSMA in different therapeutic ways, with promising results. Recent exciting work has demonstrated PSMA expression in endothelial cells of vessels restricted to the tumor-associated neo-vasculature. This finding expands the possible beneficial uses of PSMA, as new anti-PSMA mAbs continue to be developed.

...Identifiers-- ***CARCINOMA*** CELL-LINE; RADICAL PROSTATECTOMY;
MONOCLONAL-ANTIBODIES; FOLATE HYDROLASE; EXPRESSION; THERAPY;
IDENTIFICATION; LOCALIZATION; PENDETIDE; RECURRENT

12/3,K,AB/32 (Item 11 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07822737 Genuine Article#: 212BL Number of References: 43
Title: Five different anti-prostate-specific membrane
antigen (PSMA) antibodies confirm PSMA expression

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      ---  -----  -----------
? s psma or (prostate(w)specific(w)membrane(w)antigen)
            1281  PSMA
          224323  PROSTATE
         2948259  SPECIFIC
         1601197  MEMBRANE
          914405  ANTIGEN
            1490  PROSTATE(W)SPECIFIC(W)MEMBRANE(W)ANTIGEN
      S1    1887  PSMA OR (PROSTATE(W)SPECIFIC(W)MEMBRANE(W)ANTIGEN)
? s prostate
      S2  224323  PROSTATE
? s s1 and s2
            1887  S1
          224323  S2
      S3    1670  S1 AND S2
? s prognos?
      S4  672864  PROGNOS?
? s s3 and s4
            1670  S3
          672864  S4
      S5     117  S3 AND S4
? s recurren? or (biochemical(w)failure)
          592559  RECURREN?
          480687  BIOCHEMICAL
          977242  FAILURE
            1759  BIOCHEMICAL(W)FAILURE
      S6  593677  RECURREN? OR (BIOCHEMICAL(W)FAILURE)
? s s5 and s6
             117  S5
          593677  S6
      S7      28  S5 AND S6
? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
      S8      15  RD  (unique items)
? t s8/3,k,ab/1-15

 8/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2006 Dialog. All rts. reserv.

14830319   PMID: 15073252
  Influence of radioimmunoscintigraphy on postprostatectomy radiotherapy
treatment decision making.
  Jani Ashesh B; Blend Michael J; Hamilton Russell; Brendler Charles;
Pelizzari Charles; Krauz Lani; Vijayakumar Srinivasan; Sapra Bipin; Awan
Azhar; Weichselbaum Ralph R
  Department of Radiation and Cellular Oncology, University of Chicago,
Chicago, Illinois, USA. jani 1969@yahoo.com
  Journal of nuclear medicine - official publication, Society of Nuclear
Medicine (United States) Apr 2004, 45 (4) p571-8, ISSN 0161-5505--
Print Journal Code: 0217410
  Publishing Model Print; Comment in J Urol. 2005 Feb;173(2) 566; Comment
in PMID 15643257
  Document type: Clinical Trial; Journal Article; Multicenter Study;
Validation Studies
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: MEDLINE; Completed
  The aim of this study was to evaluate the role of radioimmunoscintigraphy
(RIS) directed against prostate-specific membrane
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antigen (PSMA) in influencing postradical retropubic prostatectomy (RRP) radiotherapy (RT) decision making. METHODS: The records of consecutive patients who underwent RRP, who were referred for consideration of RT, and for whom an RIS scan was obtained were reviewed. The RT decisions, with regard to (a) the decision to offer RT and (b) the general volume to be treated [prostate fossa (PF) only versus PF + pelvis (P)] before knowledge of the RIS findings were charted. The RIS findings, with regard to uptake in the PF, uptake in the P, or extrapelvic (EP) uptake were tabulated. Then, the RT treatment decisions based on the RIS knowledge were evaluated and compared with the pre-RIS RT treatment decisions. RESULTS: Of the 54 patients originally referred for post-RRP RT, the initial decision was to recommend RT to the PF only in 52 cases and to PF+P in 2 cases. The RIS findings were as follows: PF only, 43 patients; PF+P, 8 patients; PF+EP, 2 patients; PF+P+EP, 1 patient. After knowledge of these RIS results, the decision to offer RT was withdrawn in 4 of 54 patients (7.4%; P = 0.046). Furthermore, RIS changed the general treatment volume (PF only to PF+P) in 6 of 54 patients (11.1%; P = 0.015). In total, RIS altered the RT decision in 10 of 54 patients (18.5%; P = 0.0067). Three-year biochemical failure -free survival (with failure defined as 2 consecutive prostate-specific antigen [PSA] rises above 0.2 ng/mL after PSA nadir) was 78%; no patient, disease, or treatment factor reached statistical significance on univariate or multivariate analysis. CONCLUSION: RIS was found to influence post-RRP RT decision making for the identification of patients not likely to benefit from RT and for guiding general target volume definition.

The aim of this study was to evaluate the role of radioimmunoscintigraphy (RIS) directed against prostate-specific membrane antigen (PSMA) in influencing postradical retropubic prostatectomy (RRP) radiotherapy (RT) decision making. METHODS: The records of consecutive...

...to (a) the decision to offer RT and (b) the general volume to be treated [prostate fossa (PF) only versus PF + pelvis (P)] before knowledge of the RIS findings were charted...

...the RT decision in 10 of 54 patients (18.5%; P = 0.0067). Three-year biochemical failure -free survival (with failure defined as 2 consecutive ***prostate*** -specific antigen [PSA] rises above 0.2 ng/mL after PSA nadir) was 78%; no...

Descriptors: *Decision Making, Computer-Assisted; *Neoplasm Recurrence, Local--radionuclide imaging--RI; *Neoplasm Recurrence, Local--radiotherapy--RT; *Postoperative Care--methods--MT ; *Prostatic Neoplasms--radionuclide imaging--RI; *Prostatic Neoplasms --radiotherapy...
; Aged; Aged, 80 and over; Humans; Middle Aged; Neoplasm Recurrence, Local--blood--BL; Physician's Practice Patterns; Prognosis; Prostate-Specific Antigen--blood--BL; Prostatectomy; Prostatic Neoplasms--blood--BL; Prostatic Neoplasms--surgery--SU; Research Support ...

Enzyme No.: EC 3.4.21.77 (***Prostate*** -Specific Antigen)
Chemical Name: Prostate-Specific Antigen

8/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14640940 PMID: 14695135
Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer.
Ross Jeffrey S; Sheehan Christine E; Fisher Hugh A G; Kaufman Ronald P;

Kaur Prabhjot; Gray Karen; Webb Iain; Gray Gary S; Mosher Rebecca; Kallakury Bhaskar V S
Departments of Pathology and Laboratory Medicine, Albany Medical College, Albany, New York 12208, USA. rossj@mail.amc.edu
Clinical cancer research - an official journal of the American Association for Cancer Research (United States) Dec 15 2003, 9 (17) p6357-62, ISSN 1078-0432--Print Journal Code: 9502500
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
PURPOSE: The restricted expression of the surface glycoprotein prostrate-specific membrane antigen (PSMA) to normal prostate tissue, primary and metastatic prostate cancer (PCa), and the neovasculature of various nonprostatic epithelial malignancies has enabled targeting strategies for PCa treatment using anti- ***PSMA*** antibodies. EXPERIMENTAL DESIGN: Using prostatectomy specimens, immunohistochemical staining for PSMA (7E11 antibody) was performed on formalin-fixed paraffin-embedded sections of 136 cases of PCa. Cytoplasmic immunoreactivity was scored for intensity and distribution, and results were correlated with tumor grade, pathological stage, DNA ploidy status (Feulgen spectroscopy), and disease ***recurrence*** . ***PSMA*** mRNA expression in selected primary tumors and metastatic lesions was also detected using in situ hybridization and autoradiography. RESULTS: Generally, PCa cells expressed relatively increased levels of PSMA as compared with benign elements. Among the PCa cases, increased (high) ***PSMA*** expression correlated with tumor grade (P = 0.030), pathological stage (P = 0.029), aneuploidy (P = 0.010), and biochemical ***recurrence*** (P = 0.001). The mean serum ***prostate*** -specific antigen level of 18.28 ng/ml at the time of diagnosis for the PSMA-overexpressing tumors was significantly greater than the mean serum prostate-specific antigen of 9.10 ng/ml for the non-PMSA-overexpressing group (P = 0.006). On multivariate analysis, pathological stage (P = 0.018) and ***PSMA*** expression (P = 0.002) were independent predictors of biochemical ***recurrence*** . ***PSMA*** protein overexpression in high-grade primary PCa tumors and metastatic lesions also correlated with increased PSMA mRNA expression levels using in situ hybridization and autoradiography. CONCLUSIONS: This study demonstrates for the first time that overexpression of PSMA in primary PCa correlates with other adverse traditional ***prognostic*** factors and independently predicts disease outcome.

Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer.

PURPOSE: The restricted expression of the surface glycoprotein prostrate-specific membrane antigen (PSMA) to normal prostate tissue, primary and metastatic prostate cancer (PCa), and the neovasculature of various nonprostatic epithelial malignancies has enabled targeting strategies for PCa treatment using anti- ***PSMA*** antibodies. EXPERIMENTAL DESIGN: Using prostatectomy specimens, immunohistochemical staining for PSMA (7E11 antibody) was performed on formalin-fixed paraffin-embedded sections of 136 cases of PCa...

...results were correlated with tumor grade, pathological stage, DNA ploidy status (Feulgen spectroscopy), and disease ***recurrence*** . ***PSMA*** mRNA expression in selected primary tumors and metastatic lesions was also detected using in situ hybridization and autoradiography. RESULTS: Generally, PCa cells expressed relatively increased levels of PSMA as compared with benign elements. Among the PCa cases, increased (high) ***PSMA*** expression correlated with tumor grade (P = 0.030), pathological stage (P = 0.029), aneuploidy (P = 0.010), and biochemical ***recurrence*** (P = 0.001). The mean serum ***prostate*** -specific antigen level of 18.28

ng/ml at the time of diagnosis for the PSMA-overexpressing tumors was significantly greater than the mean serum prostate-specific antigen of 9.10 ng/ml for the non-PMSA-overexpressing group (P = 0.006). On multivariate analysis, pathological stage (P = 0.018) and ***PSMA*** expression (P = 0.002) were independent predictors of biochemical ***recurrence*** . ***PSMA*** protein overexpression in high-grade primary PCa tumors and metastatic lesions also correlated with increased PSMA mRNA expression levels using in situ hybridization and autoradiography. CONCLUSIONS: This study demonstrates for the first time that overexpression of PSMA in primary PCa correlates with other adverse traditional ***prognostic*** factors and independently predicts disease outcome.
...Descriptors: biosynthesis--BI; *Glutamate Carboxypeptidase II --biosynthesis--BI; *Prostatic Neoplasms--metabolism--ME; *Prostatic Neoplasms--pathology--PA; * ***Recurrence*** ...; Autoradiography; Cytoplasm --metabolism--ME; Humans; Immunohistochemistry; In Situ Hybridization; Middle Aged; Multivariate Analysis; Neoplasm Metastasis; Prognosis; RNA, Messenger--metabolism--ME; Research Support, Non-U.S. Gov't; Time Factors

8/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11/07

14135076 PMID: 15046712
Molecular markers in prostate cancer: the role in preoperative staging.
Moul Judd W; Merseburger Axel S; Srivastava Shiv
Urology Service, Department of Surgery, Walter Reed Army Medical Center, Washington, DC, USA. jmoul@cpdr.org
Clinical prostate cancer (United States) Jun 2002, 1 (1) p42-50, ISSN 1540-0352--Print Journal Code: 101155459
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Radical prostatectomy as a primary treatment for clinically localized prostate cancer has increased dramatically over the past decade due to prostate-specific antigen (PSA) screening and the awareness of the increased incidence of localized disease. Despite the stage migration to increase clinically localized disease, there are still vast numbers of men who harbor occult extraprostatic extension and develop recurrence after surgery. The study of molecular markers in the blood or tissue of surgical patients prior to treatment, called " molecular staging, " is the focus of this review. The reverse transcriptase- polymerase chain reaction (RT-PCR) test for PSA gene expression in peripheral blood or bone marrow has received considerable attention since its first report in 1992. The test detects messenger RNA species for prostate-specific/abundant genes such as PSA and prostate-specific membrane ***antigen*** . These messenger RNAs were not detected in normal blood or bone marrow, but were detected in some prostate cancer patients presumably due to circulating prostatic epithelial cells. These prostate epithelial cells are thought to be occult metastases cells, and early studies correlated a positive RT-PCR test with surgical pathology adverse features such as positive margins. Despite the many studies over the past few years, there have been inconsistent results, and the most recent studies have not been able to confirm clinical utility. Bone marrow RT-PCR has been more promising; however, it is still a research tool that needs further study. The study of molecular markers in tissue material, ie, prostate biopsy samples prior to radical prostatectomy, is problematic due to the sampling error inherent in a multifocal heterogeneous tumor such as ***prostate*** cancer. The tumor suppressor

proteins p53 and p27, Bcl-2 oncoprotein, Ki-67 proliferation index protein, E-cadherin, and microvessel density have been assessed in preradical prostatectomy needle biopsy. Results have been conflicting, and none are yet accepted as a clinically useful marker. Current and future work is focusing on analysis of multiple gene expressions or proteins simultaneously via gene chip or proteomics technology. While these expression profiles might be of value in whole prostate surgical specimens where tissues are well characterized, it is unclear how this new technology will be applied to the needle biopsy samples. Although molecular staging of radical prostatectomy patients has been under study for a decade, all assays remain research tools. Still, this area holds great promise for improving the accuracy of staging and providing a more accurate prognosis of individual men with clinically localized prostate cancer.

Molecular markers in prostate cancer: the role in preoperative staging.

Radical prostatectomy as a primary treatment for clinically localized prostate cancer has increased dramatically over the past decade due to prostate-specific antigen (PSA) screening and the awareness of the increased incidence of localized disease. Despite...

... disease, there are still vast numbers of men who harbor occult extraprostatic extension and develop ***recurrence*** after surgery. The study of molecular markers in the blood or tissue of surgical patients...
... considerable attention since its first report in 1992. The test detects messenger RNA species for prostate-specific/abundant genes such as PSA and ***prostate*** - ***specific*** ***membrane*** ***antigen***. These messenger RNAs were not detected in normal blood or bone marrow, but were detected in some prostate cancer patients presumably due to circulating prostatic epithelial cells. These ***prostate*** epithelial cells are thought to be occult metastases cells, and early studies correlated a positive...

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... gene chip or proteomics technology. While these expression profiles might be of value in whole prostate surgical specimens where tissues are well characterized, it is unclear how this new technology will...

... area holds great promise for improving the accuracy of staging and providing a more accurate prognosis of individual men with clinically localized ***prostate*** cancer.

; Disease-Free Survival; Humans; Preoperative Care; Prostate-Specific Antigen--metabolism--ME; Prostatic Neoplasms--mortality--MO; Prostatic Neoplasms--pathology--PA; Prostatic Neoplasms--surgery...

Enzyme No.: EC 3.4.21.77 (***Prostate*** -Specific Antigen)

Chemical Name: RNA, Messenger; Tumor Markers, Biological; Prostate-Specific Antigen

8/3,K,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12796086 PMID: 10906737

Value of reverse transcription polymerase chain reaction assay in

pathological stage T3N0 ***prostate*** cancer.

Okegawa T; Noda H; Kato M; Miyata A; Nutahara K; Higashihara E
Department of Urology, Kyorin University School of Medicine, Mitaka, Tokyo, Japan.

Prostate (UNITED STATES) Aug 1 2000, 44 (3) p210-8, ISSN 0270-4137 --Print Journal Code: 8101368
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

BACKGROUND: We tested the ability of the nested reverse transcription polymerase chain reaction (RT-PCR) assay to detect signs of biochemical recurrence of prostate cancer in the lymph nodes and peripheral blood of patients with pT3N0 ***prostate*** cancer. METHODS: Using lymph nodes and pre- and postoperative peripheral blood dissected from 30 patients with pT3N0 prostate cancer treated by radical prostatectomy, we used RT-PCR for prostate-specific membrane antigen (PSM) and serum prostate -specific antigen (PSA) to determine the presence of ***prostate*** cancer. Results of the nested RT-PCR assay were compared with pathological stages and biochemical ***recurrence*** . RESULTS: Two of 13 patients with capsular penetration (15%), 6 of 10 patients with invasion of seminal vesicles (60%), and 3 of 7 patients with a positive surgical margin (43%) were RT-PCR-positive for PSM and/or PSA in the lymph nodes. Results of preoperative RT-PCRs of peripheral blood for PSM and for PSA significantly differed between positive and negative results of RT-PCR in lymph nodes ($P < 0.001$ and $P < 0.001$, respectively). Results of postoperative RT-PCRs of peripheral blood for PSM and for PSA also significantly different between positive and negative results of RT-PCR in lymph nodes ($P = 0.011$ and $P = 0.001$, respectively). Nine of 11 patients with positive nested RT-PCR for PSM and/or PSA in the lymph nodes (82%) experienced biochemical ***recurrence*** . Significant difference in Kaplan-Meier ***recurrence*** -free actuarial curves was noted between patients who nested positive and negative on RT-PCR in the lymph nodes, pre- and postoperative peripheral blood, biopsy and prostatectomy Gleason score, and preoperative PSA values. In multivariate analysis, biopsy and prostatectomy Gleason score ($P = 0.026$, $P = 0.020$, respectively), pre- and postoperative RT-PCR for PSM in peripheral blood ($P = 0.030$ and $P = 0.040$, respectively), and RT-PCR for PSM in lymph nodes ($P = 0.035$) were independent ***prognostic*** factors. CONCLUSIONS: Nested RT-PCR assay of the lymph nodes or peripheral blood significantly predicted biochemical ***recurrence*** after surgery. It may help identify patients at risk for recurrence and progression of ***prostate*** cancer. Copyright 2000 Wiley-Liss, Inc.

Value of reverse transcription polymerase chain reaction assay in pathological stage T3N0 ***prostate*** cancer.

... the nested reverse transcription polymerase chain reaction (RT-PCR) assay to detect signs of biochemical recurrence of prostate cancer in the lymph nodes and peripheral blood of patients with pT3N0 ***prostate*** cancer. METHODS: Using lymph nodes and pre- and postoperative peripheral blood dissected from 30 patients with pT3N0 prostate cancer treated by radical prostatectomy, we used RT-PCR for prostate-specific membrane antigen (PSM) and serum prostate-specific antigen (PSA) to determine the presence of ***prostate*** cancer. Results of the nested RT-PCR assay were compared with pathological stages and biochemical ***recurrence*** . RESULTS: Two of 13 patients with capsular penetration (15%), 6 of 10 patients with invasion ...

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... 040, respectively), and RT-PCR for PSM in lymph nodes (P = 0.035) were independent ***prognostic*** factors. CONCLUSIONS: Nested RT-PCR assay of the lymph nodes or peripheral blood significantly predicted biochemical ***recurrence*** after surgery. It may help identify patients at risk for ***recurrence*** and progression of ***prostate*** cancer. Copyright 2000 Wiley-Liss, Inc.

Descriptors: *Antigens, Surface; *Carboxypeptidases--analysis--AN; *Neoplasm Recurrence, Local--pathology--PA; *Prostate --pathology--PA; *Prostate-Specific Antigen--analysis--AN; *Prostatic Neoplasms--pathology--PA...; Glutamate Carboxypeptidase II; Humans; Lymph Nodes--chemistry--CH; Lymph Nodes--pathology--PA; Middle Aged; Neoplasm Recurrence, Local--blood--BL; Neoplasm Recurrence, Local --diagnosis--DI; Predictive Value of Tests; Proportional Hazards Models; Prostate--chemistry--CH; Prostate-Specific Antigen--blood--BL; Prostate-Specific Antigen--genetics--GE; Prostatic Neoplasms--blood --BL; Prostatic Neoplasms--diagnosis--DI; RNA, Neoplasm--chemistry...

...Enzyme No.: II); EC 3.4.17.21 (glutamate carboxypeptidase II, human) ; EC 3.4.21.77 (***Prostate*** -Specific Antigen)

Chemical Name: Antigens, Surface; DNA, Neoplasm; RNA, Neoplasm; Carboxypeptidases; Glutamate Carboxypeptidase II; glutamate carboxypeptidase II, human; Prostate-Specific Antigen

8/3,K,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12656008 PMID: 10737491

Detection of micrometastatic prostate cancer cells in the lymph nodes by reverse transcriptase polymerase chain reaction is predictive of biochemical recurrence in pathological stage T2 prostate cancer.

Okegawa T; Nutahara K; Higashihara E

Department of Urology, Kyorin University School of Medicine, Mitaka, Tokyo, Japan.

Journal of urology (UNITED STATES) Apr 2000, 163 (4) p1183-8, ISSN 0022-5347--Print Journal Code: 0376374

Publishing Model Print; Comment in J Urol. 2000 Apr;163(4) 1189-90; Comment in PMID 10737492

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

PURPOSE: We evaluated whether detecting prostate cancer cells by the nested reverse transcriptase-polymerase chain reaction (RT-PCR) in lymph nodes has predictive value for serum prostate specific antigen (PSA) ***recurrence*** in patients undergoing radical prostatectomy. MATERIALS AND METHODS: We assessed the presence of prostate cancer cells by RT-PCR for prostate specific membrane antigen and PSA assay in lymph nodes dissected from 38 patients with localized ***prostate*** cancer treated with radical prostatectomy. The results of nested RT-PCR assay were compared with biochemical ***recurrence*** . RESULTS: Nested RT-PCR was positive in the lymph nodes of 2 of 18 patients (11%) with stage pT2a and 5 of 20 (25%) with stage pT2b disease. All 7 patients had biochemical ***recurrence*** . We noted a significant difference in the Kaplan-Meier recurrence-free actuarial probability curve in those with positive and negative nested RT-PCR results for prostate specific membrane antigen, PSA and prostate specific membrane antigen-PSA in the lymph nodes (p = 3.02x10(-7), 2.23x10(-7) and 3.02x10(-7), respectively). Multivariate analysis of serum PSA, Gleason score and preoperative RT-PCR

assay in peripheral blood showed that nested RT-PCR for prostate specific membrane antigen, PSA and prostate specific membrane antigen -PSA in the lymph nodes were independent predictors of ***recurrence*** (p = 0.0089, 0.0075 and 0.0089, respectively). CONCLUSIONS: Nested RT-PCR of the lymph nodes may be a useful pretreatment prognostic test for patients undergoing radical prostatectomy. Further research is necessary using a much larger number of patients with a longer followup.

Detection of micrometastatic prostate cancer cells in the lymph nodes by reverse transcriptase polymerase chain reaction is predictive of biochemical recurrence in pathological stage T2 prostate cancer.

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; Aged; Humans; Lymphatic Metastasis; Middle Aged; Neoplasm Recurrence, Local--blood--BL; Neoplasm Recurrence, Local --epidemiology--EP; Neoplasm Staging; Predictive Value of Tests; Prognosis; Prostate-Specific Antigen--blood--BL; Prostatectomy; Prostatic Neoplasms--blood--BL; Prostatic Neoplasms--surgery--SU; Reverse Transcriptase...

Enzyme No.: EC 3.4.21.77 (***Prostate*** -Specific Antigen)

Chemical Name: Prostate-Specific Antigen

8/3,K,AB/6 (Item 6 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

11/07

12584521 PMID: 10617892

Prostate-specific membrane antigen (PSMA): current benefits and future value.

Elgamal A A; Holmes E H; Su S L; Tino W T; Simmons S J; Peterson M; Greene T G; Boynton A L; Murphy G P

Northwest Biotherapeutics, Inc., Seattle, Washington 98134, USA. elgamal@nwbio.com

Seminars in surgical oncology (UNITED STATES) Jan-Feb 2000, 18 (1) p10-6, ISSN 8756-0437--Print Journal Code: 8503713

Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

We will review the evolution, benefits, and limitations of PSMA testing in the past, as well as its current and future value. Prostate cancer has been the most frequently diagnosed cancer and the second leading cause of cancer death in men in the United States. It has a wide spectrum of biological behavior between latent (indolent) and progressive (aggressive). Further identification of ***prostate*** - specific membrane antigen (PSMA) as a prognostic proliferation marker may enhance our understanding of the types of ***prostate*** cancer. A review of ***PSMA*** testing in the past as well as currently was conducted. Studies were reviewed that deal with detection of PSMA in serum and seminal fluid, reverse transcriptase-polymerase chain reaction (RT-PCR), immunoscintigraphy, and immunohistochemical assays. ***PSMA*** is expressed primarily in benign and cancerous prostatic epithelial cells. It is up-regulated in hormone resistant states, and in metastatic situations or other clinical situations where there is tumor ***recurrence*** or extension. Based on current results, PSMA detected in the serum by western blotting can assist in the identification, staging, and monitoring of metastatic prostate cancer. In addition, ***PSMA*** shows a promising role in directed imaging and therapy of ***recurrent*** or metastatic disease. Copyright 2000 Wiley-Liss, Inc.

Prostate-specific membrane antigen (PSMA): current benefits and future value.

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8/3,K,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12580501 PMID: 10579800

Use of artificial neural networks in evaluating prognostic factors determining the response to dendritic cells pulsed with PSMA peptides in ***prostate*** cancer patients.

Murphy G P; Snow P; Simmons S J; Tjoa B A; Rogers M K; Brandt J; Healy C G; Bolton W E; Rodbold D
Cancer Research Division, Pacific Northwest Cancer Foundation, Seattle,

Washington 98125, USA.
Prostate (UNITED STATES) Jan 2000, 42 (1) p67-72, ISSN 0270-4137--Print Journal Code: 8101368
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND: Our purpose was to compare the importance of over 22 measurements used in evaluating the clinical responses of patients with metastatic or locally recurrent prostate cancer, treated by dendritic cell (DC) infusions with prostate-specific ***membrane*** ***antigen*** (***PSMA***) peptides. METHODS: Artificial neural networks (ANNs) were employed for assessment, as well as the traditional methods of logistic regression. RESULTS: Twenty-six patients with metastatic disease and 37 patients with local recurrence were available for evaluation and comparison. ANN evaluation ranked the collective effects of DC infusion, immune responses (CD3+ cells, CD16+ cells, zeta chain+ cells), and cytokines, e.g., IL-6 and ***PSMA*** levels, very highly. Logistic regression identified all of these parameters to some degree, but in a different rank order. Patients with metastases showed a sharp rate of response secondary to the level of DC infusion, in contrast to those patients with local recurrence , in which it was more gradual. CONCLUSIONS: ANN analysis emphasizes the importance of level of DC infusion, immune parameters, cytokines, and markers such as PSMA in determining the response to ***PSMA*** peptide immunotherapy. The criteria of response were judged to be correct in 86% of metastatic patients and 83% of locally ***recurrent*** patients evaluated in this study. Copyright 2000 Wiley-Liss, Inc.

Use of artificial neural networks in evaluating prognostic factors determining the response to dendritic cells pulsed with PSMA peptides in ***prostate*** cancer patients.

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...Descriptors: drug effects--DE; *Dendritic Cells--transplantation--TR; *Neural Networks (Computer); *Peptide Fragments--therapeutic use--TU; *Prostate-Specific Antigen--therapeutic use--TU; *Prostatic Neoplasms --therapy--TH; Clinical Trials, Phase II; Humans; Immunotherapy; Neoplasm

Recurrence, Local--drug therapy--DT; Prognosis; Regression Analysis; Research Support, Non-U.S. Gov't
Enzyme No.: EC 3.4.21.77 (***Prostate*** -Specific Antigen)
Chemical Name: Peptide Fragments; Prostate-Specific Antigen

8/3,K,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12532268 PMID: 10477909
Circulating levels of interleukin-6 in patients with hormone refractory ***prostate*** cancer.
Drachenberg D E; Elgamal A A; Rowbotham R; Peterson M; Murphy G P
Pacific Northwest Cancer Foundation/Northwest Hospital, Seattle, Washington.
Prostate (UNITED STATES) Oct 1 1999, 41 (2) p127-33, ISSN 0270-4137 --Print Journal Code: 8101368
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND: Interleukin-6 (IL-6) is a cytokine that plays a central role in host defense due to its wide range of immune and hematopoietic activities. It is found in high levels in human ejaculate, and has recently been found to regulate prostate-specific protein expression in prostate cancer cells through nonsteroidal activation of the androgen receptor. IL-6 may be a candidate mediator of morbidity in patients with metastatic disease. We attempted to evaluate the potential of circulating IL-6 levels as a marker of disease progression. MATERIALS AND METHODS Serum IL-6, prostate specific antigen (PSA), percent free PSA (%fPSA), and prostate-specific membrane antigen (PSMA) were measured using commercially available assays in 407 men, including 15 controls. The rest of the study population had clinical or histologic evidence of prostate diseases, including 41 patients with chronic prostatitis, 167 with benign prostatic hyperplasia (BPH), 8 with high-grade prostatic intraepithelial neoplasia (PIN), 88 with localized prostate cancer, 22 with local recurrence after treatment of primary tumor, 4 with advanced untreated disease (nodal or bony metastases), 23 with advanced hormone dependent disease, and 39 with advanced hormone refractory disease (PSA > 1.0 ng/ml while on hormone treatment and/or evidence of disease progression). None had history of concurrent malignancy or acute inflammatory condition. Kruskal-Wallis analysis of variance and Spearman's correlation analysis were used for statistical analyses. RESULTS: Serum levels of IL-6 were significantly elevated in patients with clinically evident hormone refractory disease (5.7 +/- 1.9 pg/ml) and statistical significance was seen when comparing the elevated serum IL-6 levels to those in normal controls, prostatitis, BPH, and localized and ***recurrent*** disease, (P values < 0.01). Compared to serum levels of controls and BPH, PSA was significantly elevated in advanced untreated disease and hormone refractory groups (P < 0.05). Percent fPSA was significantly lower in all cancer patients but the hormone refractory. Serum ***PSMA*** was elevated in advanced untreated ***prostate*** cancer. Serum IL-6 showed positive correlation with PSMA and negative correlation with serum PSA but did not attain statistical significance. CONCLUSIONS: Serum IL-6 levels are significantly elevated in hormone-refractory prostate cancer patients and may be a surrogate marker of the androgen independent phenotype. Copyright 1999 Wiley-Liss, Inc.

Circulating levels of interleukin-6 in patients with hormone refractory ***prostate*** cancer.

... is found in high levels in human ejaculate, and has recently been found to regulate prostate-specific protein expression in prostate cancer cells through nonsteroidal activation of the androgen receptor. IL-6 may be a candidate...

... IL-6 levels as a marker of disease progression. MATERIALS AND METHODS Serum IL-6, prostate specific antigen (PSA), percent free PSA (%fPSA), and prostate-specific membrane antigen (PSMA) were measured using commercially available assays in 407 men, including 15 controls. The rest of the study population had clinical or histologic evidence of prostate diseases, including 41 patients with chronic prostatitis, 167 with benign prostatic hyperplasia (BPH), 8 with high-grade prostatic intraepithelial neoplasia (PIN), 88 with localized prostate cancer, 22 with local recurrence after treatment of primary tumor, 4 with advanced untreated disease (nodal or bony metastases), 23...

... elevated serum IL-6 levels to those in normal controls, prostatitis, BPH, and localized and ***recurrent*** disease, (P values < 0.01). Compared to serum levels of controls and BPH, PSA was...

...05). Percent fPSA was significantly lower in all cancer patients but the hormone refractory. Serum ***PSMA*** was elevated in advanced untreated ***prostate*** cancer. Serum IL-6 showed positive correlation with PSMA and negative correlation with serum PSA but did not attain statistical significance. CONCLUSIONS: Serum IL-6 levels are significantly elevated in hormone-refractory prostate cancer patients and may be a surrogate marker of the androgen independent phenotype. Copyright 1999...

Descriptors: *Interleukin-6--blood--BL; *Neoplasm Recurrence, Local ; *Prostatic Neoplasms--physiopathology--PP; *Tumor Markers, Biological --analysis--AN...; use--TU; Disease Progression; Humans; Interleukin-6 --pharmacology--PD; Middle Aged; Predictive Value of Tests; Prognosis ; Prostate-Specific Antigen--blood--BL; Prostatic Neoplasms--drug therapy--DT; Research Support, Non-U.S. Gov...

Enzyme No.: EC 3.4.21.77 (***Prostate*** -Specific Antigen)

Chemical Name: Antineoplastic Agents, Hormonal; Interleukin-6; Tumor Markers, Biological; Prostate-Specific Antigen

8/3,K,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12499364 PMID: 10444137

Preoperative nested reverse transcription-polymerase chain reaction for prostate specific membrane antigen predicts biochemical ***recurrence*** after radical prostatectomy.

Okegawa T; Nutahara K; Higashihara E

Department of Urology, Kyorin University School of Medicine, Mitaka, Tokyo, Japan.

BJU international (ENGLAND) Jul 1999, 84 (1) p112-7, ISSN 1464-4096 --Print Journal Code: 100886721

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

OBJECTIVE: To assess the utility of the nested reverse transcription-polymerase chain reaction (RT-PCR) method for measuring prostate specific membrane antigen (PSM) and prostate specific antigen (PSA) in predicting serum PSA ***recurrence*** after radical prostatectomy. PATIENTS AND METHODS: Nested RT-PCRs for PSM and PSA were used in 40 patients who subsequently underwent

radical prostatectomy. The accuracy of the RT-PCR assays in predicting PSA failure was compared with those for the preoperative serum PSA level, Gleason score and final pathological staging. The patients were monitored using a PSA assay (Tandem-R, Hybritech, San Diego, CA) at 3 weeks after radical prostatectomy and every 2 months thereafter. Biochemical ***recurrence*** was defined as a serum PSA level of >/=0.4 ng/mL. RESULTS: Statistical analysis indicated that the nested RT-PCR assay for PSM was the most accurate preoperative predictor of potential surgical failure (PCR-PSM, P<0.001; PCR-PSA, P=0.018; serum PSA level, P=0.149; Gleason score P=0.388, by Fisher's exact probability test). Biochemical recurrence was evaluated in relation to these methods during a mean (range) follow-up of 16.7 (6-35) months. Of the 40 patients, eight (20%, one with organ-confined cancer and seven with extraprostatic extension of cancer) developed biochemical ***recurrence*** . The Kaplan-Meier recurrence -free actuarial probability curves differed significantly between patients with positive and those with negative results for the preoperative nested RT-PCR for PSM (P<0.01, generalized Wilcoxon's test). The nested RT-PCR for PSA, preoperative serum PSA value and Gleason score were not significant predictors of biochemical ***recurrence*** (P=0.16, 0.12 and 0.24, respectively). CONCLUSIONS: The nested RT-PCR for PSM was the best preoperative predictor of biochemical recurrence among the factors examined.

Preoperative nested reverse transcription-polymerase chain reaction for prostate specific membrane antigen predicts biochemical ***recurrence*** after radical prostatectomy.

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...San Diego, CA) at 3 weeks after radical prostatectomy and every 2 months thereafter. Biochemical ***recurrence*** was defined as a serum PSA level of >/=0.4 ng/mL. RESULTS: Statistical analysis...

... P=0.149; Gleason score P=0.388, by Fisher's exact probability test). Biochemical recurrence was evaluated in relation to these methods during a mean (range) follow-up of 16...

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... for PSA, preoperative serum PSA value and Gleason score were not significant predictors of biochemical ***recurrence*** (P=0.16, 0.12 and 0.24, respectively). CONCLUSIONS: The nested RT-PCR for PSM was the best preoperative predictor of biochemical recurrence among the factors examined.

Descriptors: *Neoplasm Recurrence, Local--blood--BL; * Prostate-Specific Antigen--blood--BL; *Prostatic Neoplasms--blood--BL ; *Reverse Transcriptase Polymerase Chain Reaction; Aged; Humans; Middle Aged; Predictive Value of Tests; Prognosis; Prostatectomy; Prostatic Neoplasms--surgery--SU; Research Support, Non-U.S. Gov't

Enzyme No.: EC 3.4.21.77 (***Prostate*** -Specific Antigen)

Chemical Name: Prostate-Specific Antigen

8/3,K,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12365486 PMID: 10210369

Molecular determination of surgical margins using fossa biopsies at radical prostatectomy.

Theodorescu D; Frierson H F; Sikes R A
Department of Urology, University of Virginia Health Sciences Center, Charlottesville 22908, USA.

Journal of urology (UNITED STATES) May 1999, 161 (5) p1442-8, ISSN 0022-5347--Print Journal Code: 0376374
Publishing Model Print; Comment in J Urol. 1999 Dec;162(6) 2107; Comment in PMID 10569595
Document type: Clinical Trial; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

PURPOSE: Status of the surgical margins after radical prostatectomy is a key factor for predicting postoperative outcome. Current methods used to determine margin status are tedious, costly and vary among institutions. Sensitive and inexpensive detection of prostate cells in the circulation of patients with prostate cancer has been achieved using reverse transcriptase (RT) polymerase chain reaction (PCR) for prostate specific antigen and prostate specific ***membrane*** ***antigen*** . Therefore, we designed and tested a novel and objective molecular assay for assessing surgical margins at radical prostatectomy based on the detection of prostate specific markers using RT-PCR. We also compared this assay to standard pathological examination. MATERIALS AND METHODS: A total of 30 consecutive patients with local ***prostate*** cancer underwent radical prostatectomy. At the completion of gland excision 5 biopsies of the prostatic fossa were obtained for histopathological and molecular analysis. We performed RT-PCR analysis for prostate specific antigen and prostate specific membrane antigen messenger ribonucleic acid in these biopsy specimens, and compared the results with pathological stage. Men free of prostate cancer who underwent radical cystoprostatectomy for bladder cancer or abdominoperineal resection for rectal cancer served as controls. RESULTS: There were positive molecular margins in all patients with positive margins and/or extracapsular extension. No controls had a positive molecular assay. In 4 of 16 patients (25%) histopathological evaluation revealed organ confined disease but biopsies were positive by the molecular assay, including those in 2 (50%) who had been treated with neoadjuvant hormonal therapy before surgery because of a higher estimated risk of extracapsular disease. Results in 4 cases were uninformative. CONCLUSIONS: Our results with an objective molecular assay aimed at assessing surgical margins after radical prostatectomy reveal an excellent correlation with conventional pathological analysis. In addition, molecular assessment of the prostatic fossa identifies patients in whom extracapsular disease may have been unidentified by conventional pathological examination. In addition, this assay yields clues to why neoadjuvant hormonal treatment before radical prostatectomy does not seem to decrease the ***biochemical*** ***failure*** rate in these patients. Larger studies with longer followup are required to determine the prognostic significance of these positive molecular margins.

... determine margin status are tedious, costly and vary among institutions. Sensitive and inexpensive detection of ***prostate*** cells in the circulation of patients with prostate cancer has been achieved using reverse transcriptase (RT) polymerase chain reaction (PCR) for prostate specific antigen and prostate specific ***membrane*** ***antigen*** . Therefore, we designed and tested a novel and objective molecular assay for assessing surgical margins at radical prostatectomy based on the detection of prostate specific markers using RT-PCR. We also compared this assay to standard pathological examination. MATERIALS AND METHODS: A total of 30 consecutive patients with local ***prostate*** cancer underwent radical prostatectomy. At the completion of gland excision 5 biopsies of the prostatic fossa were

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...; Biopsy; Carboxypeptidases--blood--BL; Carboxypeptidases--genetics --GE; Comparative Study; Glutamate Carboxypeptidase II; Humans; Intraoperative Period; Prostate-Specific Antigen--blood--BL; Prostate-Specific Antigen--genetics--GE; Prostatic Neoplasms --chemistry--CH; RNA, Messenger--analysis--AN; Research Support, Non...
...Enzyme No.: II); EC 3.4.17.21 (glutamate carboxypeptidase II, human) ; EC 3.4.21.77 (***Prostate*** -Specific Antigen)
Chemical Name: Antigens, Neoplasm; Antigens, Surface; RNA, Messenger; Carboxypeptidases; Glutamate Carboxypeptidase II; glutamate carboxypeptidase II, human; Prostate-Specific Antigen

8/3,K,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12204450 PMID: 10632336
Prostate-specific membrane antigen levels in sera from healthy men and patients with benign prostate hyperplasia or ***prostate*** cancer.
Beckett M L; Cazares L H; Vlahou A; Schellhammer P F; Wright G L
Department of Microbiology and Molecular Cell Biology, Virginia Prostate Center, Eastern Virginia Medical School, Norfolk 23501, USA.
Clinical cancer research - an official journal of the American Association for Cancer Research (UNITED STATES) Dec 1999, 5 (12) p4034-40, ISSN 1078-0432--Print Journal Code: 9502500
Contract/Grant No.: CA 26659; CA; NCI; DK47754; DK; NIDDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Prostate-specific membrane antigen (PSMA) serum levels have been proposed to be of prognostic significance in patients with advanced ***prostate*** disease. The objective of the present study was to confirm PSMA serum expression by Western blot techniques, to determine whether such data could assist in the differentiation of benign from malignant prostatic disease, and to determine the suitability of serum PSMA measurements in predicting ***recurrent*** or progressive ***prostate*** malignancies. We measured PSMA, a transmembrane glycoprotein identified in prostate epithelial cells, in the sera of 236 normal individuals and cancer patients by Western blot analysis. Within the normal male population, ***PSMA*** levels increase with age and were found to be significantly elevated in subjects more than 50 years of age when compared to those of younger men. We did not confirm previous reports that serum PSMA measurements could distinguish late-stage prostate carcinoma from early-stage prostate carcinoma, nor did we find PSMA to be more effective than prostate-specific antigen in monitoring prostate cancer patient ***prognosis*** . Furthermore, we found elevated serum ***PSMA*** in healthy females, and, similar to the healthy male population, the levels

increased with age, with the highest levels found in the sera from breast cancer patients. These latter observations further support that ***PSMA*** is not a specific biomarker for prostate cancer and that a variety of normal and diseased tissue may contribute to the serum levels of ***PSMA*** .

Prostate-specific membrane antigen levels in sera from healthy men and patients with benign prostate hyperplasia or ***prostate*** cancer.
Prostate-specific membrane antigen (PSMA) serum levels have been proposed to be of prognostic significance in patients with advanced ***prostate*** disease. The objective of the present study was to confirm PSMA serum expression by Western blot techniques, to determine whether such data could assist in the differentiation of benign from malignant prostatic disease, and to determine the suitability of serum PSMA measurements in predicting ***recurrent*** or progressive ***prostate*** malignancies. We measured PSMA, a transmembrane glycoprotein identified in prostate epithelial cells, in the sera of 236 normal individuals and cancer patients by Western blot analysis. Within the normal male population, ***PSMA*** levels increase with age and were found to be significantly elevated in subjects more than...

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... levels found in the sera from breast cancer patients. These latter observations further support that PSMA is not a specific biomarker for prostate cancer and that a variety of normal and diseased tissue may contribute to the serum levels of ***PSMA*** .
; Adult; Aged; Aged, 80 and over; Comparative Study; Glutamate Carboxypeptidase II; Humans; Middle Aged; Prostate-Specific Antigen --blood--BL; Prostatic Hyperplasia--diagnosis--DI; Prostatic Neoplasms --diagnosis--DI; Prostatic Neoplasms--pathology...
...Enzyme No.: II); EC 3.4.17.21 (glutamate carboxypeptidase II, human) ; EC 3.4.21.77 (***Prostate*** -Specific Antigen)
Chemical Name: Antigens, Neoplasm; Antigens, Surface; Carboxypeptidases; Glutamate Carboxypeptidase II; glutamate carboxypeptidase II, human; Prostate-Specific Antigen

8/3,K,AB/12 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

0014169684 BIOSIS NO.: 200300126794
Prostate specific membrane antigen (PSMA):
Target validation and prognostic significance in prostate cancer (PCA).
AUTHOR: Ross J S (Reprint); Gray K; Mosher R; Deeds J; Fisher H A G; Kaur P ; Sheehan C E; Kallakury B V S
AUTHOR ADDRESS: Albany Medical College, Albany, NY, USA**USA
JOURNAL: Modern Pathology 16 (1): p167A January 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 92nd Annual Meeting of the United States and Canadian Academy of Pathology Washington, D.C., USA March 22-28, 2003; 20030322
ISSN: 0893-3952
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation

LANGUAGE: English

Prostate specific membrane antigen (PSMA):
Target validation and prognostic significance in prostate cancer (PCA).
...REGISTRY NUMBERS: ***prostate*** ***specific*** ***membrane*** antigen
DESCRIPTORS:
ORGANISMS: PARTS ETC: prostate--
DISEASES: ***prostate*** cancer...
CHEMICALS & BIOCHEMICALS: prostate specific membrane ***antigen*** { ***PSMA*** }--...

... ***prostate*** ***specific*** ***membrane*** ***antigen*** mRNA { prostate specific membrane antigen messenger RNA
MISCELLANEOUS TERMS: ...disease ***prognosis*** ; ...

...disease ***recurrence*** ; ...

...biochemical ***recurrence*** ;

8/3,K,AB/13 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

0009329439 BIOSIS NO.: 199497350724
Preoperative PSA and postoperative PSA NADIR for prediction of recurrence in patients with positive margins following radical prostatectomy
AUTHOR: Gonzalez Chris; Johannsen Lee; Lund Greg; Williams Richard
AUTHOR ADDRESS: Iowa City, IA, USA**USA
JOURNAL: Journal of Urology 151 (5 SUPPL.): p376A 1994 1994
CONFERENCE/MEETING: Eighty-ninth Annual Meeting of the American Urological Association San Francisco, California, USA May 14-19, 1994; 19940514
ISSN: 0022-5347
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

Preoperative PSA and postoperative PSA NADIR for prediction of recurrence in patients with positive margins following radical prostatectomy
DESCRIPTORS:
MISCELLANEOUS TERMS: ... ***PROGNOSIS*** ; ...

... ***PROSTATE*** SPECIFIC ANTIGEN...
... ***PROSTATE*** ***SPECIFIC*** ***MEMBRANE*** ***ANTIGEN*** ;

8/3,K,AB/14 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

13491435 Genuine Article#: 884TC Number of References: 59
Title: Molecular staging by RT-PCR analysis for PSA and PSMA in peripheral blood and bone marrow samples is an independent predictor of time to biochemical failure following radical prostatectomy for clinically localized prostate cancer (ABSTRACT AVAILABLE)
Author(s): Mitsiades C; Lembessis P; Sourla A; Milathianakis C; Tsintavis A ; Koutsilieris M (REPRINT)
Corporate Source: Univ Athens,Sch Med, Dept Expt Physiol,75 Micras Asias

St/Goudi 11527//Greece/ (REPRINT); Univ Athens,Sch Med, Dept Expt Physiol,Goudi 11527//Greece/; Harvard Univ,Sch Med, Dana Farber Canc Inst, Dept Med Oncol,Boston//MA/02115; Diagnost & Therapeut Med Ctr,Endo OncoRes Labs,Athens//Greece/; Metaxa Anticanc Hosp,Dept Urol,Piraeus//Greece/(mkouts@medscape.com)

Journal: CLINICAL & EXPERIMENTAL METASTASIS, 2004, V21, N6, P495-505
ISSN: 0262-0898 Publication date: 20040000
Publisher: KLUWER ACADEMIC PUBL, VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT, NETHERLANDS
Language: English Document Type: ARTICLE

Abstract: Radical prostatectomy should ideally be curative for all patients with clinically localized prostate cancer (PrCa), yet a sizeable proportion of them eventually relapse. We examined in this setting the feasibility of pre-operative risk stratification for early post-operative relapse using reverse transcriptase polymerase chain reaction (RT-PCR) for prostate-specific antigen (PSA) and prostate-specific membrane antigen (PSMA) transcripts in pre-operative bone marrow (BM) biopsies and peripheral blood (PBL) samples. Nested RT-PCR for PSA and ***PSMA*** transcripts were performed in RNA from BM biopsies and PBL samples prospectively obtained from 111 men newly diagnosed, by trans-rectal ultrasound (TRUS)-guided biopsy, with clinically localized PrCa and scheduled to undergo radical prostatectomy, according to their respective doctors' recommendation. Molecular analysis for each sample (PBL or BM) was considered positive only if both PSA and PSMA transcripts were detectable. Serial serum PSA level measurements served for biochemical follow-up and detection of ***biochemical*** ***failure*** (PSA >0.2 ng/ml). PBL and BM RT-PCR molecular staging delineated three groups of patients (a) PBL-BM- (72 patients, 65%), (b) PBL+BM+ (29 patients, 26%), and (c) PBL+BM- (10 patients, 9%). These three groups corresponded to low, high, and intermediate risk for early post-prostatectomy recurrence (median time to biochemical ***failure*** of >38, 8, and >28 months, respectively). Multivariate analysis confirmed that molecular staging status was independent predictor of disease-free survival, after adjusting for PSA levels and Gleason score. In clinically localized PrCa, combined PSA/ ***PSMA*** RT-PCR in PBL and BM is an independent predictor of time to ***biochemical*** ***failure*** following radical prostatectomy.

Title: Molecular staging by RT-PCR analysis for PSA and PSMA in peripheral blood and bone marrow samples is an independent predictor of time to biochemical failure following radical prostatectomy for clinically localized prostate cancer

Abstract: Radical prostatectomy should ideally be curative for all patients with clinically localized prostate cancer (PrCa), yet a sizeable proportion of them eventually relapse. We examined in this setting...

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...Identifiers--POLYMERASE-CHAIN-REACTION; DIGITAL RECTAL EXAMINATION; HORMONAL-THERAPY PRIOR; MEMBRANE ANTIGEN; PATHOLOGICAL STAGE; GLEASON SCORE; PROGNOSTIC-SIGNIFICANCE; NEOADJUVANT THERAPY; EUROPEAN EXPERIENCE; DISEASE RECURRENCE

8/3,K,AB/15 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10723795 Genuine Article#: 561LJ Number of References: 36
Title: Reverse transcription-polymerase chain reaction detection of prostate-specific antigen, prostate-specific membrane antigen, and prostate stem cell antigen in one milliliter of peripheral blood: Value for the staging of prostate cancer (ABSTRACT AVAILABLE)
Author(s): Hara N; Kasahara T; Kawasaki T; Bilim V; Obara K; Takahashi K; Tomita Y (REPRINT)
Corporate Source: Niigata Univ,Div Mol Oncol, Dept Signal Transduction Res, Grad Sch Med & Dent Sci,Asahimachi 1/Niigata 951//Japan/ (REPRINT); Niigata Univ,Div Mol Oncol, Dept Signal Transduction Res, Grad Sch Med & Dent Sci,Niigata 951//Japan/; Niigata Univ,Div Urol, Dept Regenerat & Transplant Med, Grad Sch Med & Dent Sci,Niigata 951//Japan/
Journal: CLINICAL CANCER RESEARCH, 2002, V8, N6 (JUN), P1794-1799
ISSN: 1078-0432 Publication date: 20020600
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202 USA
Language: English Document Type: ARTICLE
Abstract: Purpose: There have been several studies on the presence of circulating tumor cells in the peripheral blood of patients with malignant tumors including prostate cancer (PCa) using reverse transcription-PCR (RT-PCR). One of the aims of these studies was to obtain high sensitivity that would enable early-stage diagnosis. However, they varied in their detection rates, and the methods were rather complicated. We have improved the RT-PCR assay combining three prostate-associated molecules, prostate specific antigen (PSA), prostate specific membrane antigen (PSMA), and prostate stem cell antigen (PSCA) to reveal patients with poor ***prognosis*** .

Experimental Design: Peripheral blood samples were obtained from 129 patients including 58 cases of PCa and 71 cases of nonmalignant disorders. Total RNA was extracted from 1 ml of whole blood using a commercially available kit.

Results: The sensitivity of PSA-, PSMA-, and PSCA-nested RT-PCR was verified with positive signals of a single LNCaP cell in I ml of female blood sample. PSA-, ***PSMA*** -, and PSCA-mRNA were detected in 7 (12.1%), 12 (20.7%), and 8 (13.8%) PCa, and in 1, 2, and 0 samples in nonmalignant disorders, respectively. Among 58 PCa patients, each PCR indicated the prognostic value in the hierarchy of PSCA>PSA>PSMA RT-PCR, and extraprostatic cases with positive PSCA PCR indicated lower disease-progression-free survival than those with negative PSCA PCR.

Conclusions: The present findings suggest that PSCA PCR would be most promising for the molecular staging of PCa. The present RT-PCR is a highly cost-effective and rapid procedure, enabling the molecular staging of PCa with RT-PCR as a diagnostic routine.

Title: Reverse transcription-polymerase chain reaction detection of prostate-specific antigen, prostate-specific membrane antigen, and prostate stem cell antigen in one milliliter of peripheral blood: Value for the staging of prostate cancer

...Abstract: presence of circulating tumor cells in the peripheral blood of patients with malignant tumors including prostate cancer (PCa) using reverse transcription-PCR (RT-PCR). One of the aims of these studies...

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...1 ml of whole blood using a commercially available kit.

Results: The sensitivity of PSA-, PSMA-, and PSCA-nested RT-PCR was verified with positive signals of a single LNCaP cell in I ml of female blood sample. PSA-, ***PSMA*** -, and PSCA-mRNA were detected in 7 (12.1%), 12 (20.7%), and 8 (13...

...and 0 samples in nonmalignant disorders, respectively. Among 58 PCa patients, each PCR indicated the prognostic value in the hierarchy of PSCA>PSA>PSMA RT-PCR, and extraprostatic cases with positive PSCA PCR indicated lower disease-progression-free survival...

...Identifiers--POSITIVE CELLS; REACTION ASSAY; RT-PCR; RADICAL PROSTATECTOMY; FLOW-CYTOMETRY; FOLLOW-UP; EXPRESSION; RECURRENCE; METASTASIS; ADULT

? ds

Set	Items	Description
S1	1887	PSMA OR (PROSTATE(W)SPECIFIC(W)MEMBRANE(W)ANTIGEN)
S2	224323	PROSTATE
S3	1670	S1 AND S2
S4	672864	PROGNOS?
S5	117	S3 AND S4
S6	593677	RECURREN? OR (BIOCHEMICAL(W)FAILURE)
S7	28	S5 AND S6
S8	15	RD (unique items)

?

```
      ---  -----  -----------
? s psma or (prostate(w)specific(w)membrane(w)antigen)
            1281  PSMA
          224323  PROSTATE
         2948259  SPECIFIC
         1601197  MEMBRANE
          914405  ANTIGEN
            1490  PROSTATE(W)SPECIFIC(W)MEMBRANE(W)ANTIGEN
      S1    1887  PSMA OR (PROSTATE(W)SPECIFIC(W)MEMBRANE(W)ANTIGEN)
? s recurren? or relaps?
          592559  RECURREN?
          174683  RELAPS?
      S2  727770  RECURREN? OR RELAPS?
? s s1 and s2
            1887  S1
          727770  S2
      S3     137  S1 AND S2
? s prostate
      S4  224323  PROSTATE
? s s3 and s4
             137  S3
          224323  S4
      S5     134  S3 AND S4
? s predict? or risk?
         1673318  PREDICT?
         1890893  RISK?
      S6 3331375  PREDICT? OR RISK?
? s s5 and s6
             134  S5
         3331375  S6
      S7      59  S5 AND S6
? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
      S8      35  RD  (unique items)
? s s8 and py>2003
              35  S8
         7599699  PY>2003
      S9      13  S8 AND PY>2003
? t s9/3,k,ab/1-13

 9/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2006 Dialog. All rts. reserv.

21991895   PMID: 16841802
   Prostate-specific  membrane  antigen  expression
  ***predicts***     ***prostate***   cancer   ***recurrence***
  Oncology  (Williston  Park,  N.Y.) (United  States)   Jun   ***2006***   ,  20
 (7)  p790,  ISSN 0890-9091--Print   Journal Code: 8712059
  Publishing Model Print
  Document type: News
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: MEDLINE; Completed

   Prostate-specific  membrane  antigen  expression
  ***predicts***     ***prostate***   cancer   ***recurrence***
  ...  ***2006***  ,
  Descriptors:      *Antigens,      Surface--metabolism--ME;     *Glutamate
Carboxypeptidase   II--metabolism--ME;  *Neoplasm  Recurrence,  Local
```

--diagnosis--DI; *Prostatic Neoplasms--metabolism--ME; Humans; Predictive Value of Tests; Prostatic Neoplasms--diagnosis--DI

9/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

21701795 PMID: 16607370
Technology insight: monoclonal antibody imaging of ***prostate*** cancer.
Bander Neil H
New York-Presbyterian Hospital, Weill Medical College of Cornell University, New York, NY 10021, USA. nhbander@med.cornell.edu
Nature clinical practice. Urology (United States) Apr ***2006*** , 3 (4) p216-25, ISSN 1743-4270--Print Journal Code: 101226508
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Imaging is a critical component of diagnosis, staging and monitoring, all of which factor heavily in treatment decision-making for cancer patients. Agents, such as antibodies, can target molecules that are relatively unique to cancer cells. ***Prostate*** - ***specific*** ***membrane*** ***antigen*** (PSMA) is the most well-established, highly restricted ***prostate*** -cancer-related cell membrane antigen known. Ten years ago, the FDA approved (111)In-capromab pendetide for use in imaging soft-tissue, but not bone, sites of metastatic prostate cancer for presurgical staging or the evaluation of PSA ***relapse*** after local therapy. For presurgical patients with high-risk disease but negative bone, CT and MRI scans, capromab demonstrated the ability to identify some patients with positive nodes, thereby sparing them an unnecessary surgical procedure. But there have been no follow-up studies to indicate that high-risk patients with a negative capromab scan have a lower failure rate after surgery. In the setting of PSA ***relapse*** , capromab is compromised by its inability to sensitively image bone metastases; bone is the first site of metastatic ***prostate*** cancer in 72% of patients. The problem with imaging bone metastases is that capromab detects an antigenic site on the intracellular portion of PSMA-a site not accessible to circulating antibodies. Early results indicate that second-generation antibodies that target the extracellular domain of PSMA might provide significant benefits in the imaging of ***prostate*** cancer.

Technology insight: monoclonal antibody imaging of ***prostate*** cancer.
... ***2006*** ,
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...unnecessary surgical procedure. But there have been no follow-up studies to indicate that high-risk patients with a negative capromab scan have a lower failure rate after surgery. In the setting of PSA relapse , capromab is compromised by its inability to sensitively image bone metastases; bone is the first site of metastatic prostate cancer in 72% of patients. The problem with imaging bone metastases is that

capromab detects an antigenic site on the intracellular portion of ***PSMA*** -a site not accessible to circulating antibodies. Early results indicate that second-generation antibodies that target the extracellular domain of PSMA might provide significant benefits in the imaging of ***prostate*** cancer.
; Bone Neoplasms--diagnosis--DI; Bone Neoplasms--secondary--SC; Humans; Indicators and Reagents; Neoplasm Recurrence, Local--diagnosis--DI; Prostate-Specific Antigen--blood--BL; Prostatic Neoplasms--blood--BL
Enzyme No.: EC 3.4.21.77 (***Prostate*** -Specific Antigen)
Chemical Name: Antibodies, Monoclonal; Indicators and Reagents; Capromab Pendetide; Prostate-Specific Antigen

9/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

21654114 PMID: 16985928
ProstaScint(R) Scan: Contemporary Use in Clinical Practice.
Taneja Samir S
Reviews in urology (United States) 2004, 6 Suppl 10 pS19-28, ISSN 1523-6161--Print Journal Code: 100889067
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Data Review
Indium In 111 capromab pendetide (ProstaScint(R); Cytogen Corporation, Princeton, NJ), a radiolabeled monoclonal antibody to prostate-specific membrane antigen , offers a potential means of localizing sites of soft tissue metastasis in prostate cancer patients. Although the test was previously limited by poor positive predictive value and specificity owing to the inherent limitations of single photon emission computed tomography, improvements in techniques of anatomic localization, along with increased reader experience, have significantly improved its accuracy. In addition to the conventional roles for ProstaScint, such as staging and detection of relapse, a number of new potential applications have emerged.
... ***2004*** ,
... In 111 capromab pendetide (ProstaScint(R); Cytogen Corporation, Princeton, NJ), a radiolabeled monoclonal antibody to prostate-specific membrane antigen , offers a potential means of localizing sites of soft tissue metastasis in prostate cancer patients. Although the test was previously limited by poor positive predictive value and specificity owing to the inherent limitations of single photon emission computed tomography, improvements...

...accuracy. In addition to the conventional roles for ProstaScint, such as staging and detection of relapse , a number of new potential applications have emerged.

9/3,K,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

15244740 PMID: 15679047
Molecular staging by RT-pCR analysis for PSA and PSMA in peripheral blood and bone marrow samples is an independent predictor of time to biochemical failure following radical prostatectomy for clinically localized ***prostate*** cancer.
Mitsiades Constantine S; Lembessis Peter; Sourla Antigone; Milathianakis Constantine; Tsintavis Athanassios; Koutsilieris Michael

Department of Experimental Physiology, Medical School, University of Athens, Goudi-Athens, Greece.
Clinical & experimental metastasis (Netherlands) 2004, 21 (6) p495-505, ISSN 0262-0898--Print Journal Code: 8409970
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Radical prostatectomy should ideally be curative for all patients with clinically localized prostate cancer (PrCa), yet a sizeable proportion of them eventually ***relapse*** . We examined in this setting the feasibility of pre-operative risk stratification for early post-operative relapse using reverse transcriptase polymerase chain reaction (RT-PCR) for prostate-specific antigen (PSA) and prostate-specific membrane antigen (PSMA) transcripts in preoperative bone marrow (BM) biopsies and peripheral blood (PBL) samples. Nested RT-PCR for PSA and ***PSMA*** transcripts were performed in RNA from BM biopsies and PBL samples prospectively obtained from 111 men newly diagnosed, by trans-rectal ultrasound (TRUS)-guided biopsy, with clinically localized PrCa and scheduled to undergo radical prostatectomy, according to their respective doctors' recommendation. Molecular analysis for each sample (PBL or BM) was considered positive only if both PSA and ***PSMA*** transcripts were detectable. Serial serum PSA level measurements served for biochemical follow-up and detection of biochemical failure (PSA >0.2 ng/ml). PBL and BM RT-PCR molecular staging delineated three groups of patients (a) PBL-BM- (72 patients, 65%), (b) PBL+BM+ (29 patients, 26%), and (c) PBL+BM- (10 patients, 9%). These three groups corresponded to low, high, and intermediate risk for early post-prostatectomy recurrence (median time to biochemical failure of >38, 8, and >28 months, respectively). Multivariate analysis confirmed that molecular staging status was independent predictor of disease-free survival, after adjusting for PSA levels and Gleason score. In clinically localized PrCa, combined PSA/PSMA RT-PCR in PBL and BM is an independent predictor of time to biochemical failure following radical prostatectomy.

Molecular staging by RT-pCR analysis for PSA and PSMA in peripheral blood and bone marrow samples is an independent predictor of time to biochemical failure following radical prostatectomy for clinically localized ***prostate*** cancer.

... ***2004*** ,

Radical prostatectomy should ideally be curative for all patients with clinically localized prostate cancer (PrCa), yet a sizeable proportion of them eventually ***relapse*** . We examined in this setting the feasibility of pre-operative risk stratification for early post-operative relapse using reverse transcriptase polymerase chain reaction (RT-PCR) for prostate-specific antigen (PSA) and prostate-specific membrane antigen (PSMA) transcripts in preoperative bone marrow (BM) biopsies and peripheral blood (PBL) samples. Nested RT-PCR for PSA and ***PSMA*** transcripts were performed in RNA from BM biopsies and PBL samples prospectively obtained from 111...

... analysis for each sample (PBL or BM) was considered positive only if both PSA and ***PSMA*** transcripts were detectable. Serial serum PSA level measurements served for biochemical follow-up and detection...

... c) PBL+BM- (10 patients, 9%). These three groups corresponded to low, high, and intermediate risk for early post-prostatectomy recurrence (median time to biochemical failure of >38, 8, and >28 months, respectively). Multivariate analysis confirmed that molecular staging status was independent predictor of disease-free survival, after adjusting for PSA levels and Gleason score. In clinically localized

PrCa, combined PSA/PSMA RT-PCR in PBL and BM is an independent predictor of time to biochemical failure following radical prostatectomy.

Descriptors: *Antigens, Surface--blood--BL; *Glutamate Carboxypeptidase II--blood--BL; *Prostate-Specific Antigen--blood--BL; *Prostatic Neoplasms--blood--BL; Bone Marrow--metabolism--ME; Disease-Free Survival; Feasibility Studies; Humans; Neoplasm Staging; Predictive Value of Tests; Prostatectomy; Prostatic Neoplasms--pathology--PA; Prostatic Neoplasms--surgery--SU; Research Support, Non...

...Enzyme No.: II); EC 3.4.17.21 (glutamate carboxypeptidase II, human) ; EC 3.4.21.77 (***Prostate*** -Specific Antigen)

Chemical Name: Antigens, Surface; Glutamate Carboxypeptidase II; glutamate carboxypeptidase II, human; Prostate-Specific Antigen

9/3,K,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14960454 PMID: 15225091

Role of ProstaScint for brachytherapy in localized prostate adenocarcinoma.

Ellis Rodney J; Kim Edward; Foor Ryan

Aultman Hospital, Department of Radiation Oncology, Canton, OH 44710, USA. rellis@aultman.com

Expert review of molecular diagnostics (England) Jul 2004, 4 (4) p435-41, ISSN 1473-7159--Print Journal Code: 101120777

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

ProstaScint (CYT-356 or capromab pendetide, Cytogen) is an 111In-labeled monoclonal mouse antibody specific for prostate-specific membrane antigen, a prostate transmembrane glycoprotein that is upregulated in ***prostate*** adenocarcinoma. ProstaScint scans are US Food and Drug Administration approved for pretreatment evaluation of metastatic disease in high- ***risk*** patients. They are also approved for post-prostatectomy assessment of recurrent disease in patients with a rising ***prostate*** -specific antigen level. This review explores the literature on ProstaScint and its use in guiding the treatment of ***prostate*** cancer. A novel technique for identifying areas of cancer within the prostate using ProstaScint images fused with pelvic computed tomography scans is also described. The identification of areas of high antibody signal provides targets for radiotherapeutic dose escalation, with the overall goals of improving treatment outcome while preserving adjacent tissue structures and decreasing treatment morbidity. Copyright Future Drugs Ltd.

Role of ProstaScint for brachytherapy in localized prostate adenocarcinoma.

... ***2004*** ,

...CYT-356 or capromab pendetide, Cytogen) is an 111In-labeled monoclonal mouse antibody specific for prostate-specific membrane antigen, a prostate transmembrane glycoprotein that is upregulated in ***prostate*** adenocarcinoma. ProstaScint scans are US Food and Drug Administration approved for pretreatment evaluation of metastatic disease in high- ***risk*** patients. They are also approved for post-prostatectomy assessment of recurrent disease in patients with a rising ***prostate*** -specific antigen level. This review explores the literature on ProstaScint and its use in guiding the treatment of ***prostate*** cancer. A novel technique for identifying areas of cancer within the prostate using ProstaScint images fused with pelvic

computed tomography scans is also described. The identification of...

9/3,K,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2006 Dialog. All rts. reserv.

11/07

14953002 PMID: 15217924
Detection of prostate cancer and predicting progression: current and future diagnostic markers.
Tricoli James V; Schoenfeldt Mason; Conley Barbara A
Diagnostics Research Branch, Cancer Diagnosis Program, National Cancer Institute, Rockville, Maryland, USA. tricolij@mail.nci.nih.gov
Clinical cancer research - an official journal of the American Association for Cancer Research (United States) Jun 15 2004, 10 (12 Pt 1) p3943-53, ISSN 1078-0432--Print Journal Code: 9502500
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Carcinoma of the prostate is the second leading cause of male cancer-related death in the United States. Better indicators of prostate cancer presence and progression are needed to avoid unnecessary treatment, predict disease course, and develop more effective therapy. Numerous molecular markers have been described in human serum, urine, seminal fluid, and histological specimens that exhibit varying capacities to detect prostate cancer and predict disease course. However, to date, few of these markers have been adequately validated for clinical use. The purpose of this review is to examine the current status of these markers in prostate cancer and to assess the diagnostic potential for future markers from identified genes and molecules that display loss, mutation, or alteration in expression between tumor and normal ***prostate*** tissues. In this review we cite 91 molecular markers that display some level of correlation with prostate cancer presence, disease progression, cancer recurrence, prediction of response to therapy, and/or disease-free survival. We suggest criteria to consider when selecting a marker for further development as a clinical tool and discuss five examples of markers (chromogranin A, glutathione S-transferase pi 1, prostate stem cell antigen, prostate-specific membrane antigen , and telomerase reverse transcriptase) that fulfill some of these criteria. Finally, we discuss how to conduct evaluations of candidate prostate cancer markers and some of the issues involved in the validation process.

Detection of prostate cancer and predicting progression: current and future diagnostic markers.
... ***2004*** ,
Carcinoma of the prostate is the second leading cause of male cancer-related death in the United States. Better indicators of prostate cancer presence and progression are needed to avoid unnecessary treatment, predict disease course, and develop more effective therapy. Numerous molecular markers have been described in human serum, urine, seminal fluid, and histological specimens that exhibit varying capacities to detect prostate cancer and predict disease course. However, to date, few of these markers have been adequately validated for clinical...

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9/3,K,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14830319 PMID: 15073252

Influence of radioimmunoscintigraphy on postprostatectomy radiotherapy treatment decision making.

Jani Ashesh B; Blend Michael J; Hamilton Russell; Brendler Charles; Pelizzari Charles; Krauz Lani; Vijayakumar Srinivasan; Sapra Bipin; Awan Azhar; Weichselbaum Ralph R

Department of Radiation and Cellular Oncology, University of Chicago, Chicago, Illinois, USA. jani 1969@yahoo.com

Journal of nuclear medicine - official publication, Society of Nuclear Medicine (United States) Apr 2004, 45 (4) p571-8, ISSN 0161-5505--Print Journal Code: 0217410

Publishing Model Print; Comment in J Urol. 2005 Feb;173(2) 566; Comment in PMID 15643257

Document type: Clinical Trial; Journal Article; Multicenter Study; Validation Studies

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

The aim of this study was to evaluate the role of radioimmunoscintigraphy (RIS) directed against prostate-specific membrane antigen (PSMA) in influencing postradical retropubic prostatectomy (RRP) radiotherapy (RT) decision making. METHODS: The records of consecutive patients who underwent RRP, who were referred for consideration of RT, and for whom an RIS scan was obtained were reviewed. The RT decisions, with regard to (a) the decision to offer RT and (b) the general volume to be treated [prostate fossa (PF) only versus PF + pelvis (P)] before knowledge of the RIS findings were charted. The RIS findings, with regard to uptake in the PF, uptake in the P, or extrapelvic (EP) uptake were tabulated. Then, the RT treatment decisions based on the RIS knowledge were evaluated and compared with the pre-RIS RT treatment decisions. RESULTS: Of the 54 patients originally referred for post-RRP RT, the initial decision was to recommend RT to the PF only in 52 cases and to PF+P in 2 cases. The RIS findings were as follows: PF only, 43 patients; PF+P, 8 patients; PF+EP, 2 patients; PF+P+EP, 1 patient. After knowledge of these RIS results, the decision to offer RT was withdrawn in 4 of 54 patients (7.4%; P = 0.046). Furthermore, RIS changed the general treatment volume (PF only to PF+P) in 6 of 54 patients (11.1%; P = 0.015). In total, RIS altered the RT decision in 10 of 54 patients (18.5%; P = 0.0067). Three-year biochemical failure-free survival (with failure defined as 2 consecutive ***prostate*** -specific antigen [PSA] rises above 0.2 ng/mL after PSA nadir) was 78%; no patient, disease, or treatment factor reached statistical significance on univariate or multivariate analysis. CONCLUSION: RIS was found to influence post-RRP RT decision making for the identification of patients not likely to benefit from RT and for guiding general target volume definition.

... ***2004*** ,
The aim of this study was to evaluate the role of radioimmunoscintigraphy (RIS) directed against prostate-specific membrane antigen (PSMA) in influencing postradical retropubic prostatectomy (RRP) radiotherapy (RT) decision making. METHODS: The records of consecutive...

...to (a) the decision to offer RT and (b) the general volume to be treated [prostate fossa (PF) only versus PF + pelvis (P)] before knowledge of the RIS findings were charted...

... P = 0.0067). Three-year biochemical failure-free survival (with failure defined as 2 consecutive prostate-specific antigen [PSA] rises above 0.2 ng/mL after PSA nadir) was 78%; no...
Descriptors: *Decision Making, Computer-Assisted; *Neoplasm Recurrence, Local--radionuclide imaging--RI; *Neoplasm Recurrence, Local--radiotherapy--RT; *Postoperative Care--methods--MT ; *Prostatic Neoplasms--radionuclide imaging--RI; *Prostatic Neoplasms --radiotherapy--RT; *Radioimmunodetection--methods--MT; *Risk Assessment--methods--MT; Aged; Aged, 80 and over; Humans; Middle Aged; Neoplasm Recurrence, Local--blood--BL; Physician's Practice Patterns; Prognosis; Prostate-Specific Antigen--blood--BL; Prostatectomy; Prostatic Neoplasms--blood--BL; Prostatic Neoplasms--surgery--SU; Research Support...
Enzyme No.: EC 3.4.21.77 (***Prostate*** -Specific Antigen)
Chemical Name: Prostate-Specific Antigen

9/3,K,AB/8 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

0016037177 BIOSIS NO.: 200600382572
Prostate-specific membrane antigen (PSMA)
expression as a predictor of prostate cancer progression
AUTHOR: Hofer Matthias D (Reprint); Perner Sven; Li Haojie; Kuefer Rainer; Hautmann Richard E; Gschwend Juergen E; Moeller Peter; Rubin Mark A
JOURNAL: Journal of Urology 175 (4, Suppl. S): p155-156 APR 2006
2006
CONFERENCE/MEETING: Annual Meeting of the American-Urological-Association Atlanta, GA, USA May 20 -25, 2006; 20060520
SPONSOR: Amer Urolog Assoc
ISSN: 0022-5347
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

Prostate-specific membrane antigen (PSMA)
expression as a predictor of prostate cancer progression
2006
...REGISTRY NUMBERS: ***prostate*** - ***specific*** ***membrane*** antigen
...ENZYME COMMISSION NUMBER: ***prostate*** - ***specific*** ***membrane*** antigen
DESCRIPTORS:
ORGANISMS: PARTS ETC: prostate--
DISEASES: ***prostate*** cancer...
CHEMICALS & BIOCHEMICALS: prostate-specific membrane antigen {PSMA}--
MISCELLANEOUS TERMS: ...disease ***recurrence*** ;

9/3,K,AB/9 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

14013316 Genuine Article#: 934AF Number of References: 26
Title: Imaging with radiolabelled monoclonal antibody (MUJ591) to prostate-specific membrane antigen in staging of clinically localized prostatic carcinoma: comparison with clinical, surgical and histological staging (ABSTRACT AVAILABLE)
Author(s): Nargund V (REPRINT) ; Al Hashmi D; Kumar P; Gordon S; Otitie U; Ellison D; Carroll M; Baithun S; Britton KE
Corporate Source: St Bartholomews Hosp,Dept Urol,King George V Bldg/London EC1A 7BE//England/ (REPRINT); Univ London,St Bartholomews Hosp & Barts, Dept Urol,London//England/; Univ London,St Bartholomews Hosp & Barts, Dept Nucl Med,London//England/; Univ London,St Bartholomews Hosp & Barts, Dept Pathol,London//England/; Univ London,London Queen Mary Sch Med,London//England/(virod.nargund@bartsandthelondon.nhs.uk)
Journal: BJU INTERNATIONAL, 2005, V95, N9 (JUN), P1232-1236
ISSN: 1464-4096 Publication date: 20050600
Publisher: BLACKWELL PUBLISHING, 9600 GARSINGTON RD, OXFORD OX4 2DG, OXON, ENGLAND
Language: English Document Type: ARTICLE
Abstract: OBJECTIVE

To evaluate the reliability of prostate scintigraphy using a radiolabelled antibody (MUJ591) raised against the external domain of prostate-specific membrane antigen [PSMA) in the staging of early prostate cancer,

PATIENTS AND METHODS

This was a prospective study of 16 patients who had radical retropubic prostatectomies (median PSA 9.75 ng/mL). All patients underwent PSMA imaging using MUJ591 radiolabelled with Tc-99m using a photoreduction technique.

RESULTS The findings of prostate imaging and histology were identical in seven patients. Scans showed understaging and overstaging in six and three patients, respectively.

CONCLUSIONS PSMA scintigraphy using Tc-99m-labelled MUJ591 identifies the presence of prostate cancer, but is not sensitive in delineating micro-invasion of the capsule, seminal vesicles or bladder neck. As in other studies it seems to be useful in detecting ***prostate*** bed ***recurrence*** and distant micrometastasis.

Title: Imaging with radiolabelled monoclonal antibody (MUJ591) to prostate-specific membrane antigen in staging of clinically localized prostatic carcinoma: comparison with clinical, surgical and histological staging
, 2005
Abstract: OBJECTIVE

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...Identifiers-- ***PREDICT*** PATHOLOGICAL STAGE; RADICAL PROSTATECTOMY; EXTRACELLULAR DOMAIN; GLEASON SCORE; CANCER; ADENOCARCINOMA; SPECIMEN; CYT-351

9/3,K,AB/10 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

13828817 Genuine Article#: 915VF Number of References: 45
Title: Use of multiple biomarkers for a molecular diagnosis of prostate cancer (ABSTRACT AVAILABLE)
Author(s): Landers KA; Burger MJ; Tebay MA; Purdie DM; Scells B; Samaratunga H; Lavin MF; Gardiner RA (REPRINT)
Corporate Source: Univ Queensland,Cent Clin Div, Dept Surg, Sch Med,Herston/Qld 4072/Australia/ (REPRINT); Univ Queensland,Cent Clin Div, Dept Surg, Sch Med,Herston/Qld 4072/Australia/; Queensland Inst Med Res,Herston/Qld/Australia/; Sullivan & Nicolaides Pathol,Taringa/Qld/Australia/; Royal Brisbane Hosp,Herston/Qld/Australia/(f.gardiner@mailbox.uq.edu.au)
Journal: INTERNATIONAL JOURNAL OF CANCER, 2005, V114, N6 (MAY 10), P 950-956
ISSN: 0020-7136 Publication date: 20050510
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 111 RIVER ST, HOBOKEN, NJ 07030 USA
Language: English Document Type: ARTICLE
Abstract: The identification of biomarkers capable of providing a reliable molecular diagnostic test for prostate cancer (PCa) is highly desirabie clinically. We describe here 4 biomarkers, UDP-N-Acetyl-alpha-D-galactosamine transferase (GalNAc-T3; not previously associated with PCa), PSMA, Hepsin and DD3/PCA3, which, in combination, distinguish prostate cancer from benign ***prostate*** hyperplasia (BPH). GalNAc-T3 was identified as overexpressed in PCa tissues by microarray analysis, confirmed by quantitative real-time PCR and shown immunohistochemically to be localised to prostate epithelial cells with higher expression in malignant cells. Real-time quantitative PCR analysis across 21 PCa and 34 BPH tissues showed 4.6-fold overexpression of GalNAc-T3 (p = 0.005). The noncoding mRNA (DD3/PCA3) was overexpressed 140-fold (p = 0.007) in the cancer samples compared to BPH tissues. Hepsin was overexpressed 21-fold (p = 0.049, whereas the overexpression for ***PSMA*** was 66-fold (p = 0.047). When the gene expression data for these 4 biomarkers was combined in a logistic regression model, a predictive index was obtained that distinguished 100% of the PCa samples from all of the BPH samples. Therefore, combining these genes in a real-time PCR assay represents a powerful new approach to diagnosing PCa by molecular profiling. (c) 2005 Wiley-Liss, Inc.

Title: Use of multiple biomarkers for a molecular diagnosis of prostate cancer
, 2005
Abstract: The identification of biomarkers capable of providing a reliable molecular diagnostic test for prostate cancer (PCa) is highly

desirabie clinically. We describe here 4 biomarkers, UDP-N-Acetyl-alpha-D-galactosamine transferase (GalNAc-T3; not previously associated with PCa), PSMA, Hepsin and DD3/PCA3, which, in combination, distinguish prostate cancer from benign ***prostate*** hyperplasia (BPH). GalNAc-T3 was identified as overexpressed in PCa tissues by microarray analysis, confirmed by quantitative real-time PCR and shown immunohistochemically to be localised to prostate epithelial cells with higher expression in malignant cells. Real-time quantitative PCR analysis across 21...

...to BPH tissues. Hepsin was overexpressed 21-fold (p = 0.049, whereas the overexpression for ***PSMA*** was 66-fold (p = 0.047). When the gene expression data for these 4 biomarkers was combined in a logistic regression model, a predictive index was obtained that distinguished 100% of the PCa samples from all of the BPH...
...Identifiers--ALPHA-D-GALACTOSAMINE; N-ACETYLGALACTOSAMINYL TRANSFERASE-3; ENDOTHELIAL GROWTH-FACTOR; MEMBRANE ANTIGEN; GENE-EXPRESSION; BIOCHEMICAL RECURRENCE; CELLS; CLONING; ADENOCARCINOMA; PROTEASE

9/3,K,AB/11 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

12932555 Genuine Article#: 835KP Number of References: 29
Title: Role of ProstaScint (R) for brachytherapy in localized prostate adenocarcinoma (ABSTRACT AVAILABLE)
Author(s): Ellis R (REPRINT) ; Kim E; Foor R
Corporate Source: Aultman Hosp,Dept Radiat Oncol,Canton//OH/44710 (REPRINT) ; Aultman Hosp,Dept Radiat Oncol,Canton//OH/44710; Case Western Reserve Univ,Sch Med,Cleveland//OH/44106; Univ Hosp Cleveland,Dept Radiat Oncol,Cleveland//OH/44106; Ohio Univ,Sch Med,Athens//OH/45701(rellis@aulonan.com)
Journal: EXPERT REVIEW OF MOLECULAR DIAGNOSTICS, 2004, V4, N4 (JUL) , P435-441
ISSN: 1473-7159 Publication date: 20040700
Publisher: FUTURE DRUGS LTD, UNITEC HOUSE, 3RD FL, 2 ALBERT PLACE, FINCHLEYY CENTRAL, LONDON N3 1QB, ENGLAND
Language: English Document Type: REVIEW
Abstract: ProstaScint(R) (CYT-356 or capromab pendetide, Cytogen) Is an In-111-labeled monoclonal mouse antibody specific for prostate-specific membrane antigen, a prostate transmembrane glycoprotein that Is upregulated In prostate adenocarcinoma. Prostascint scans are US Food and Drug Administration approved for pretreatment evaluation of metastatic disease In high-***risk*** patients. They are also approved for post-prostatectomy assessment of recurrent disease In patients with a rising ***prostate*** -specific antigen level. This review explores the literature on ProstaScint and Its use In guiding the treatment of ***prostate*** cancer. A novel technique for Identifying areas of cancer within the prostate using ProstaScint Images fused with pelvic computed tomography scans Is also described: The Identification of areas of high antibody signal provides targets for radiotherapeutic dose escalation, with the overall goals of Improving treatment outcome while preserving adjacent tissue structures and decreasing treatment morbidity.

Title: Role of ProstaScint (R) for brachytherapy in localized prostate adenocarcinoma
, 2004
...Abstract: 356 or capromab pendetide, Cytogen) Is an In-111-labeled monoclonal mouse antibody specific for prostate-specific

membrane antigen, a prostate transmembrane glycoprotein that Is upregulated In ***prostate*** adenocarcinoma. Prostascint scans are US Food and Drug Administration approved for pretreatment evaluation of metastatic disease In high-risk patients. They are also approved for post-prostatectomy assessment of recurrent disease In patients with a rising prostate -specific antigen level. This review explores the literature on ProstaScint and Its use In guiding the treatment of prostate cancer. A novel technique for Identifying areas of cancer within the prostate using ProstaScint Images fused with pelvic computed tomography scans Is also described. The Identification of...

9/3,K,AB/12 (Item 1 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 11075311 IFI Acc No: 2006-0024316
IFI Publication Control No: 2006-0024316 IFI Chemical Acc No: 2006-0005151
Document Type: C
PROSTATIC CANCER VACCINE
Inventors: Maida Anthony E III (US); Spitler Lynn E (US)
Assignee: Unassigned Or Assigned To Individual
Assignee Code: 68000
Attorney, Agent or Firm: MORRISON & FOERSTER LLP, 12531 HIGH BLUFF DRIVE, SUITE 100, SAN DIEGO, CA, 92130-2040, US
Publication (No,Kind,Date), Applic (No,Date):
US 20060024316 A1 20060202 US 200542514 20050124
Priority Applic(No,Date): US 200542514 20050124; US 94288057 19940810; US 99300978 19990428; US 93105444 19930811

Abstract: Vaccines capable of eliciting an immune antitumor response for ***prostate*** tumors are disclosed. The active ingredient in such vaccines is selected from the group consisting of at least one antigen over-represented in the prostate gland or an immunologically effective portion thereof; an expression system capable of generating in situ said antigen or portion; a naked DNA encoding such antigen and portion; and an anti-idiotypic antibody or fragment thereof which mimics said antigen or portion.

Publication (No,Kind,Date), Applic (No,Date):
... ***20060202***

Abstract: Vaccines capable of eliciting an immune antitumor response for ***prostate*** tumors are disclosed. The active ingredient in such vaccines is selected from the group consisting of at least one antigen over-represented in the prostate gland or an immunologically effective portion thereof; an expression system capable of generating in situ...

Exemplary Claim:
1. A method to induce an antitumor cellular immune response in a potential or actual prostate tumor-bearing subject which method comprises administering to said subject a composition comprising an ingredient...

...and is selected from the group consisting of at least one antigen overrepresented in the prostate gland or an immunologically effective portion thereof; or an expression system capable of generating in...

...said composition induces said cellular immune response to at least one

antigen overrepresented in the ***prostate*** gland.
Non-exemplary Claims:
...of claim 2, wherein said protein or peptide is selected from the group consisting of prostate specific antigen (PSA), prostate specific membrane antigen (PSMA), prostatic acid phosphatase (PAP), and an immunologically effective portion thereof...

...4. The method of claim 1, wherein said subject is afflicted with metastatic ***prostate*** cancer...
...1, wherein said subject has been surgically treated to excise said tumor but is at ***risk*** for ***recurrence*** .
...

...1, wherein said composition is administered to said subject prior to surgical excision of said ***prostate*** tumor...

...7. The method of claim 1, wherein said subject is a potential ***prostate*** tumor-bearing subject at ***risk*** for said tumor.

9/3,K,AB/13 (Item 2 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 10706956 IFI Acc No: 2004-0214204
IFI Publication Control No: 2004-0214204 IFI Chemical Acc No: 2004-0059770
Document Type: C
METHODS OF DIAGNOSING AND TREATING CANCER; USING PROSTATE SPECIFIC MEMBRANE ANTIGEN EXPRESSION TO DIAGNOSE RECURRENCE OF CELL PROLIFERATIVE DISORDERS
Inventors: Ross Jeffrey S (US)
Assignee: Unassigned Or Assigned To Individual
Assignee Code: 68000
Probable Assignee: Millennium Pharmaceuticals Inc
Attorney, Agent or Firm: FISH & RICHARDSON PC, 225 FRANKLIN ST, BOSTON, MA, 02110, US
Publication (No,Kind,Date), Applic (No,Date):
US 20040214204 A1 20041028 US 2003736112 20031215
Priority Applic(No,Date): US 2003736112 20031215
Provisional Applic(No,Date): US 60-439205 20030110

Abstract: The invention features methods of evaluating the risk of cancer ***recurrence*** in a subject diagnosed with cancer.

...USING ***PROSTATE*** ***SPECIFIC*** ***MEMBRANE*** ***ANTIGEN*** EXPRESSION TO DIAGNOSE RECURRENCE OF CELL PROLIFERATIVE DISORDERS
Publication (No,Kind,Date), Applic (No,Date):
... ***20041028***

Abstract: The invention features methods of evaluating the risk of cancer ***recurrence*** in a subject diagnosed with cancer.

Exemplary Claim:
...A W I N G

1. A method of determining if a subject is at ***risk*** for prostate cancer recurrence, the method comprising: providing a sample from a subject; and determining PSMA expression levels in the sample, wherein increased PSMA expression levels relative to a reference standard are indicative of a risk of prostate cancer recurrence, to thereby determine if the subject is at ***risk*** of ***prostate*** cancer ***recurrence*** .
Non-exemplary Claims:

2. The method of claim 1, wherein the subject is diagnosed with ***prostate*** cancer...

...3. The method of claim 1, wherein the increased ***PSMA*** levels are increased relative to a reference standard...

...4. The method of claim 1, wherein the reference standard is ***PSMA*** expression levels in a control subject diagnosed with prostate cancer...

...11. The method of claim 1, wherein the ***risk*** of ***recurrence*** is determined upon diagnosis of ***prostate*** cancer...

...12. The method of claim 1, wherein the ***risk*** of ***recurrence*** is determined after the subject is diagnosed with ***prostate*** cancer...

...13. The method of claim 1, wherein the ***risk*** of ***recurrence*** is determined after the subject has been treated with an anti-cancer treatment...

...15. The method of claim 1, wherein ***PSMA*** expression levels are determined by determining the ***PSMA*** protein levels in a sample...

...16. The method of claim 15, wherein ***PSMA*** protein levels are determined by a method selected from the group consisting of an enzyme ...

...17. The method of claim 1, wherein ***PSMA*** expression levels are determined by determining the PSMA nucleic acid levels in a sample ...

...18. The method of claim 17, wherein ***PSMA*** nucleic acid levels are determined by a method selected from the group consisting of Northern...

...19. The method of claim 1, further comprising selecting a treatment for a subject at ***risk*** for ***recurrence*** .
...

...26. The method of claim 24, wherein the antibody therapy comprises administration of an anti PSMA antibody that binds the extracellular domain of ***PSMA*** .
...

...30. The method of claim 28, wherein the subject has ***prostate*** cancer, and the treatments are: a. a partial or radical prostatectomy, and b. one or...
...wherein the antibody therapy is administration of an antibody that binds the extracellular domain of ***PSMA*** .
...

...not have a higher level of expression is assigned a value of 40% or less ***risk*** of ***recurrence*** .
...

...not have a higher level of expression is assigned a value of 30% or less ***risk*** of ***recurrence*** .
...

...The method of claim 1, further comprising selecting a treatment for the subject wherein the ***risk*** of ***recurrence*** is low...

...37. The method of claim 35, wherein the ***risk*** of ***recurrence*** is less than 40...

...38. The method of claim 35, wherein the ***risk*** of ***recurrence*** is less than 30...

...40. The method of claim 1, comprising: determining ***PSMA*** expression levels in a plurality of subjects, wherein increased PSMA expression levels are indicative of a risk of cancer recurrence; and selecting a subset of the plurality of subjects having increased expression levels for administration
?

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11/9/06

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From: Davis, Minh-Tam
Sent: Tuesday, November 07, 2006 1:24 PM
To: STIC-ILL
Subject: REPRINT REQUEST FOR 10/736112

1) 08130245 Genuine Article#: 249PV Number of References: 38
Title: Prostate-specific membrane antigen: Much more than a prostate cancer marker (ABSTRACT AVAILABLE)
Author(s): Chang SS; Gaudin PB; Reuter VE; OKeefe DS; Bacich DJ; Heston WDW (REPRINT)
Corporate Source: MEM SLOAN KETTERING CANC CTR,GEORGE M OBRIEN UROL RES CTR, 1275 YORK AVE/NEW YORK//NY/10021 (REPRINT); MEM SLOAN KETTERING CANC CTR,GEORGE M OBRIEN UROL RES CTR/NEW YORK//NY/10021; MEM SLOAN KETTERING CANC CTR,DEPT PATHOL/NEW YORK//NY/10021
Journal: MOLECULAR UROLOGY, 1999, V3, N3 (FAL), P313-319
ISSN: 1091-5362 Publication date: 19990900

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Thank you.

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ART UNIT 1642, ROOM 3A24, MB 3C18
272-0830

Ab to live prostate cancer cells

MOLECULAR UROLOGY
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Mary Ann Liebert, Inc.

Prostate-Specific Membrane Antigen: Much More Than a Prostate Cancer Marker

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DENISE S. O'KEEFE,[1] DEAN J. BACICH,[1] and W.D.W. HESTON, PH.D.[1]

ABSTRACT

Prostate cancer continues to be the most common cancer and second leading cause of cancer-related death among men. The use of markers, particularly serum-based prostate specific antigen (PSA), has contributed to the rapid rise in diagnosed cases in the late 1980s and early 1990s, but new diagnostic and possible therapeutic markers are needed and are currently being evaluated. One of these, prostate-specific membrane antigen (PSMA), is an approximately 100-kDa type II transmembrane protein originally thought to be highly selectively expressed in all types of prostatic tissue, with expression being upregulated in androgen-depleted or androgen-independent states. The radioimmunoconjugate form of the anti-PSMA monoclonal antibody (mAb) 7E11 is currently being used to diagnose prostate cancer metastasis and recurrence. In addition, Phase I and II trials have started utilizing PSMA in different therapeutic ways, with promising results. Recent exciting work has demonstrated PSMA expression in endothelial cells of vessels restricted to the tumor-associated neovasculature. This finding expands the possible beneficial uses of PSMA, as new anti-PSMA mAbs continue to be developed.

INTRODUCTION

PROSTATE-SPECIFIC MEMBRANE ANTIGEN (PSMA) is a type II membrane protein originally characterized by the monoclonal antibody (mAb) 7E11 and found to be expressed in all types of prostate tissue, including benign epithelium, benign prostatic hyperplasia (BPH), prostatic intraepithelial neoplasia (PIN), and carcinoma.[1–5] Its expression has been studied on the mRNA transcript level by RNAse protection assay and the protein level by Western blot and immunohistochemistry staining with 7E11. After some dispute, two groups have recently confirmed the location of the PSMA gene on the short arm of chromosome 11.[6,7] Two variations of the PSMA protein, designated PSMA and the spliced variant PSM′, have been described, but their individual roles have not been definitively elucidated.[8]

Currently, new strategies for utilizing PSMA for the diagnosis and treatment of prostate cancer are being explored. The possible role of PSMA continues to expand, as recent studies have demonstrated that PSMA is selectively expressed in tumor-associated neovasculature. Thus, its usefulness may extend to nonprostatic malignancies. This article briefly reviews present and possible future diagnostic and therapeutic options for the use of PSMA.

NEW ANTIBODIES TO PSMA

For a period of time, 7E11 was the only available anti-PSMA mAb. It binds an intracellular epitope near the amino terminus, specifically a 6-amino acid segment.[9] Recently, however, Liu et al have developed four anti-PSMA mAbs (J591, J533, J415, E99) each of which binds to a different location on the extracellular PSMA domain. Researchers at Hybritech, Inc., have also developed an extracellular domain-binding antibody, PEQ226.5, as well as PM2J004.5, which binds an intracellular PSMA epitope separate and distinct from that bound by 7E11.[10] The interest in developing new antibodies to the PSMA external domain is due in large part to the fact that the internal domain-binding anti-PSMA mAbs; e.g., 7E11 and PM2J004.5, do not bind viable cells.[11–13] This inability to bind live cells makes the currently available 7E11 mAb a less attractive option for in vivo purposes.

[1]George M. O'Brien Urology Research Center and [2]Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York.

PSMA FUNCTIONS

Folate Hydrolase

The PSMA protein has unique folate hydrolase activity, initially discovered in PSMA-expressing LNCaP cells. Pinto et al[14] demonstrated that LNCaP cells had the ability to remove the terminal glutamates sequentially from folate if they are gamma linked. Cell lines such as PC-3 and DU145 that do not express PSMA do not have this hydrolytic capability.[14] The ability of PSMA to act as a novel folate hydrolase may allow its use in a prodrug activation strategy utilizing, for example, triglutamylmethotrexate (MTX Glu_3). Thus, any cell that expresses PSMA would allow entry of the MTX Glu_3 by cleaving the glutamates, causing the cytotoxic MTX to accumulate.[15]

Neurocarboxypeptidase

The PSMA protein has also been found to simulate the activity of a rat brain neurocarboxypeptidase. Work by Carter et al[16] identified a partial cDNA from a rat brain protein that had 86% homology with a region of the PSMA gene. They found that LNCaP cells express the same enzyme activity as does the rat brain protein. This rat brain enzyme is a neurocarboxypeptidase that cleaves alpha-linked glutamates from N-acetylaspartylglutamate.[16,17] In the human prostate, there are neuroendocrine and secretory cells. Determination of their function with respect to glutamate or neuropeptides requires more research.

PSMA EXPRESSION IN CELL CULTURE AND HUMAN TISSUE

Prostate Cancer Cell Lines

In live LNCaP cells that express PSMA, the mAbs that bind the internal domain of PSMA do not react with the viable cells. Only after fixation with Formalin do these internal domain-binding mAbs demonstrate reactivity with the cell lines.[11–13] This requirement for recognition of an intracellular epitope probably plays a significant role in their inability to react with live cells and may make them less appropriate for in vivo strategies aimed at either diagnosis or treatment. The recently developed anti-PSMA mAbs that bind the external domain do bind to live as well as fixed cells, and this ability makes them more attractive for future purposes (Fig. 1).[12,13]

Human Prostate Tissue

Studies have consistently demonstrated 7E11-positive staining in a variety of prostatic tissues.[4,5] The immunoreactivity is present in a higher percentage and with a stronger intensity in

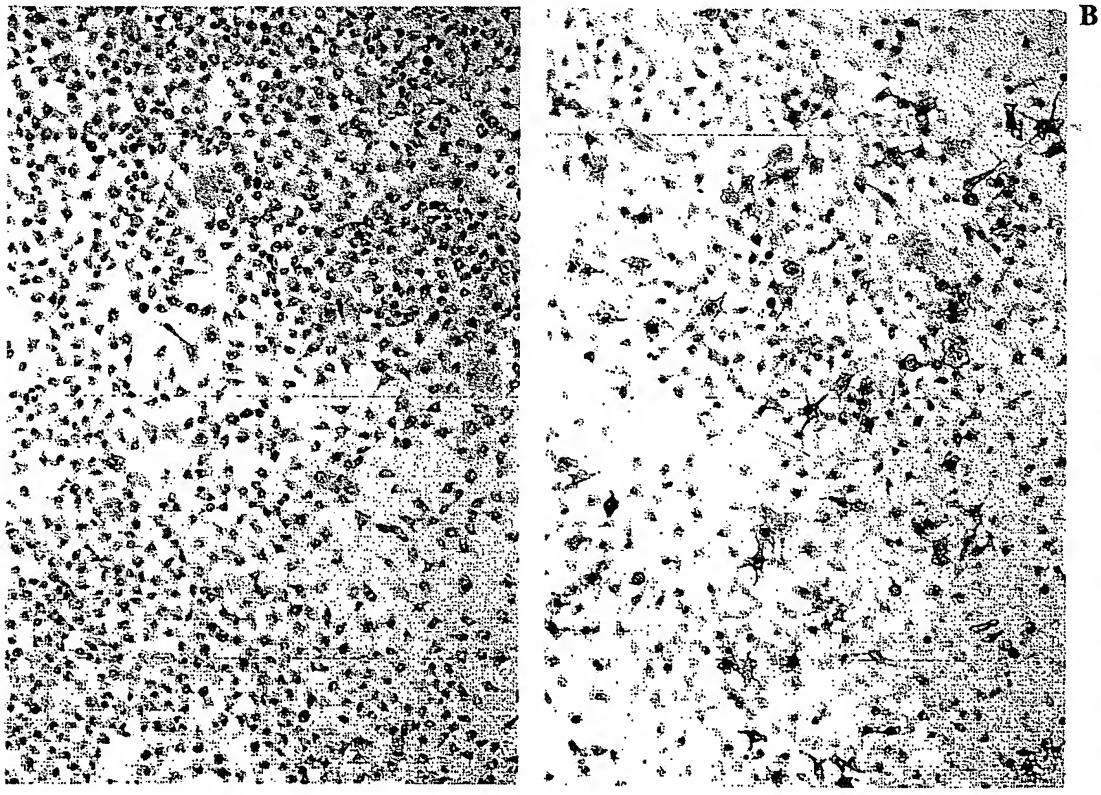

FIG. 1. Comparative immunohistochemical reactivity in viable PC3-PIP cells that express PSMA. **(A)** The mAb 7E11 (internal PSMA domain) is without reactivity. **(B)** The J591 (external PSMA domain) mAb shows binding.

PIN and cancer cells than in benign epithelial cells.[1,2,5] The binding occurs in the secretory-acinar epithelium; basal epithelium and stromal cells have been PSMA negative (Fig. 2). In the largest and most recent series, Bostwick et al[18] showed positive immunoreactivity in all 184 prostate specimens that they examined and scored. In addition, an incremental increase in the percentage of staining was noted from benign epithelial tissue (69.5% of cells positive) to high-grade PIN (77.9% of cells positive) to malignant cells (80.2% of cells positive).[18] We have demonstrated similar staining with the 7E11 mAb and with previously uncompared anti-PSMA mAbs J591, J415, PM2J004.5, and PEQ226.5 in all the prostate samples examined.[13]

Human Benign Tissue: Several Nonprostatic Organs Express PSMA

Although PMSA is highly expressed in prostatic tissue, several other tissue types have shown reactivity with the mAb 7E11, albeit inconsistently. On an mRNA transcript level, Israeli et al, who used a ribonuclease protection assay, demonstrated in frozen human tissue that there is PSMA expression in the brain, salivary gland, and small bowel but not in muscle, kidney, liver, or mammary gland.[3] Troyer et al, using Western blot analysis, examined frozen human tissue and also did not find expression in skeletal muscle, cardiac muscle, kidney, liver, breast, or colon.[9] These findings differ from those of immunohistochemcial studies. Horoszewicz et al demonstrated reactivity with the proximal tubule cells of the kidney but no reactivity with small intestine, colon, skeletal muscle, heart, brain, or breast.[1] In paraffin-fixed tissue, Silver et al demonstrated antibody binding to duodenum, proximal renal tubule cells, and neuroendocrine cells of the colon but observed no binding to brain, skeletal muscle, parotid, breast, or normal vasculature.[4] Differing methods of tissue preparation have been indicated as a possible cause for these variations in 7E11 binding, and these studies utilized only the 7E11 mAb.

Recent work involving 7E11 but also including other anti-PSMA mAbs consistently have demonstrated binding in duodenal epithelial (brush border) cells and proximal tubule cells in the kidney.[12,13] The proximal small bowel, specifically the duodenum, is known to have high folate hydrolase activity. Activity of this enzyme on the luminal border is consistent with staining by the mAbs in the brush border of the duodenum, which utilizes this enzymatic activity for absorbing folates from ingested food. The proximal tubule cells of the kidney also have a known role in folate reabsorption in their apical membrane. This role in folate metabolism may explain the binding of the anti-PSMA mAbs to these tissues.

The mAb 7E11 also has reacted with a portion of skeletal muscle cells. None of the other mAbs reacted with skeletal muscle. The reason for this reactivity remains unknown, but it likely represents some type of nonspecific binding.[12,13]

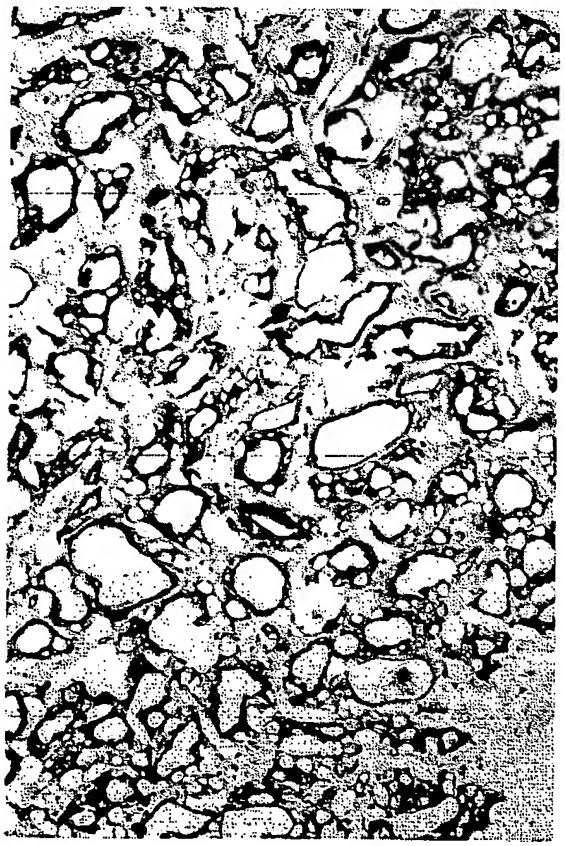

FIG. 2. Prostatic tissue staining with anti-PSMA mAb 7E11. Staining occurs in secretory cells, not in stromal tissue.

Human Malignant Tissue: Tumor-Associated Neovasculature Expresses PSMA

No previous study has demonstrated 7E11 reactivity with vascular endothelial cells in benign tissues, even in those tissues that do demonstrate PSMA expression, such as kidney. However, reactivity of the anti-PSMA mAbs with the endothelium of malignant tissue neovasculature has been demonstrated by 7E11 imunohistochemistry staining. This reactivity was first detected by Silver et al, who demonstrated what they described as "neoexpression of PSMA in endothelial cells" of vessels associated with certain tumors, including renal-cell cancer (unspecified type), transitional-cell carcinoma of the bladder, and colon carcinoma. Those investigators found no 7E11 binding to the tumor cells of these paraffin-embedded specimens.[4] Recently, Liu et al noted reactivity with the tumor-associated vasculature in all 23 nonprostatic carcinomas studied, which included renal, urothelial, and lung, as well as adenocarcinoma metastatic to the liver. These investigators examined immunohistochemical reactivity by using, in addition to 7E11, the four anti-PSMA mAbs that they developed, which bind the external domain of PSMA.[12] We have also examined a large number of carcinomas, including conventional (clear-cell) renal-cell cancer, transitional-cell lesions of the bladder, testicular-embryonal, neuroendocrine, colon, and breast; and the different types of malignancies consistently and strongly expressed PSMA (Fig. 3).[13] In immunohistochemistry staining, we used

five anti-PSMA mAbs, and we confirmed their binding to tumor-associated neovascular endothelial cells by using CD34 binding in sequential tissue sections. The antiendothelial-cell mAb CD34, which has been used extensively in the analysis of tumor angiogenesis and microvessel density, served as a positive control that verified PSMA expression in endothelial cells. Vessels in noncancerous tissue did not display immunoreactivity, and the vasculature of the corresponding benign tissue samples likewise did not demonstrate PSMA expression. Similarly, the different malignant cells and the vessels in noncancerous tissue did not demonstrate binding.

This binding to the neovasculature associated with solid malignancies does not seem to occur in prostate cancer. Silver et al noted that the cancer specimens they examined with 7E11 stained strongly in the prostate cells but not in the vascular endothelial cells.[4] Similarly, in their review of radical prostatectomy specimens, Bostwick et al did not see 7E11 reactivity in the vascular endothelium.[18] As in previous studies, we also could not demonstrate consistent binding of these mAbs to the tumor-associated neovasculature in prostate cancer (unpublished observations). The reason for the lack of reactivity in prostate cancer remains unclear and could be multifactorial. The prostate does not classically have an impressive angiogenic characteristic compared with many solid malignancies and does not incite an impressive stromal desmoplastic response. This lack of response may inhibit PSMA expression. There also may be other inhibitory factors associated with prostate cancer or prostatic tissue.

MODULATION OF PSMA EXPRESSION

Previous in vitro data demonstrated PSMA upregulation in cells grown in an androgen-deprived state. Israeli et al demonstrated that LNCaP cells incubated with dihydrotestosterone (DHT) had low PSMA expression, whereas those cells grown in an androgen-stripped medium displayed significantly increased PSMA expression.[3] Retrospectively examining 20 specimens from prostate cancer patients treated by castration or long-term androgen deprivation, Wright et al found that 11 specimens had increased PSMA reactivity after the loss of androgens.[19] Using a PSMA-derived RNA probe in in situ hybridization studies, Kawakami el al revealed increased PSMA expression in prostate specimens from patients with hormone-refractory disease, as well as in specimens with higher Gleason scores.[20] In contrast to PSA's direct correlation with androgen levels, PSMA expression appears inversely related to androgen levels. Thus, manipulation of patients' androgen levels during treatment may affect PSMA expression.

With these findings, we hypothesized that a short course of neoadjuvant androgen deprivation, although not shown to produce an overall or disease-free survival benefit,[21,22] may increase PSMA expression. This response would make PSMA a more accessible target for novel prodrug antibody-based therapy. We have examined more than 20 radical prostatectomy specimens from patients who received neoadjuvant androgen deprivation (ADT/RRP) and have compared them with specimens from a similar cohort of patients who underwent radical retropubic prostatectomy (RRP) alone. Our preliminary data did not demonstrate an increase in PSMA expression in the ADT/RRP group, even in the cancerous portion of the specimens: no significant differences in staining intensity or percentage of cells stained were seen between the ADT/RRP groups and the RRP-alone group.[23] At least two explanations for this finding are plausible. One is the short (3-month) course of androgen deprivation. Differences in PSMA expression may not have been significant at this time or may have been too subtle to delineate on an immunohistochemical level. Second, the predominantly well-differentiated tumors represented by these specimens may not be the most likely to demonstrate a change in PSMA expression.

CLINICAL APPLICATIONS OF PSMA

Diagnostic Utility

Currently, the mAb 7E11 has been modified by linkage with ^{111}indium to produce a radiodiagnostic marker, ^{111}In capromab pendetide, for prostate cancer recurrence and metastasis. The radiographic test, marketed under the name ProstaScint (Cytogen, Princeton, NJ) gained Food and Drug Administration approval in early 1997. Clinical trials have demonstrated both few adverse effects and the clinical utility of this radioimmunoconjugate in identifying prostatic cancer recurrence, both local and distant.[24–27] In an early study by Kahn et al, 27 patients with rising PSA values after radical prostatectomy underwent Prostascint scans. Of these patients, 22 had lesions evident on the scan, 11 of which were confirmed by other means.[28] In a follow-up study, 183 patients were examined in a similar situation, and once again, 50% of the positive scans were confirmed, this time by biopsy alone.[26] The majority of studies show a sensitivity of 60% to 80% and a specificity of 70% to 90% for this noninvasive method of detecting malignant prostatic disease. Recently, an incidental renal-cell carcinoma was discovered by a positive ^{111}Incapromab pendetide scan.[29] This example confirms the recognition by the anti-PSMA mAb 7E11 of tumor-associated neovasculature. More research is necessary to determine the efficacy of anti-PSMA mAbs in diagnosing and possibly treating (e.g., with a therapeutic isotope such as yttrium-90) nonprostatic malignant disease by binding the tumor-associated neovasculature.

Therapeutic Uses

Currently, the PSMA protein is being utilized in several novel treatments for prostatic cancer. One method involves immunotherapy, an attractive option that avoids foreign DNA or various vectors but rather uses the patient's own cells. Gong et al have developed a unique approach involving creation of an artificial T-cell receptor that modifies human T cells genetically so that they target cells expressing PSMA. This artificial T-cell receptor incorporates a PSMA-specific single-chain antibody fused to a zeta-chain signal-transduction domain. In vitro results are promising, with lysis of PSMA-positive prostate cancer cells. In addition, there was impressive proliferation of these modified T cells in response to the presence of PSMA-expressing cells that was augmented by costimulation. In vivo trials are currently in progress.[30] Tjoa et al recently reported follow-up on Phase I and Phase II trials utilizing PSMA peptides to help generate an immune response by infusing dendritic cells

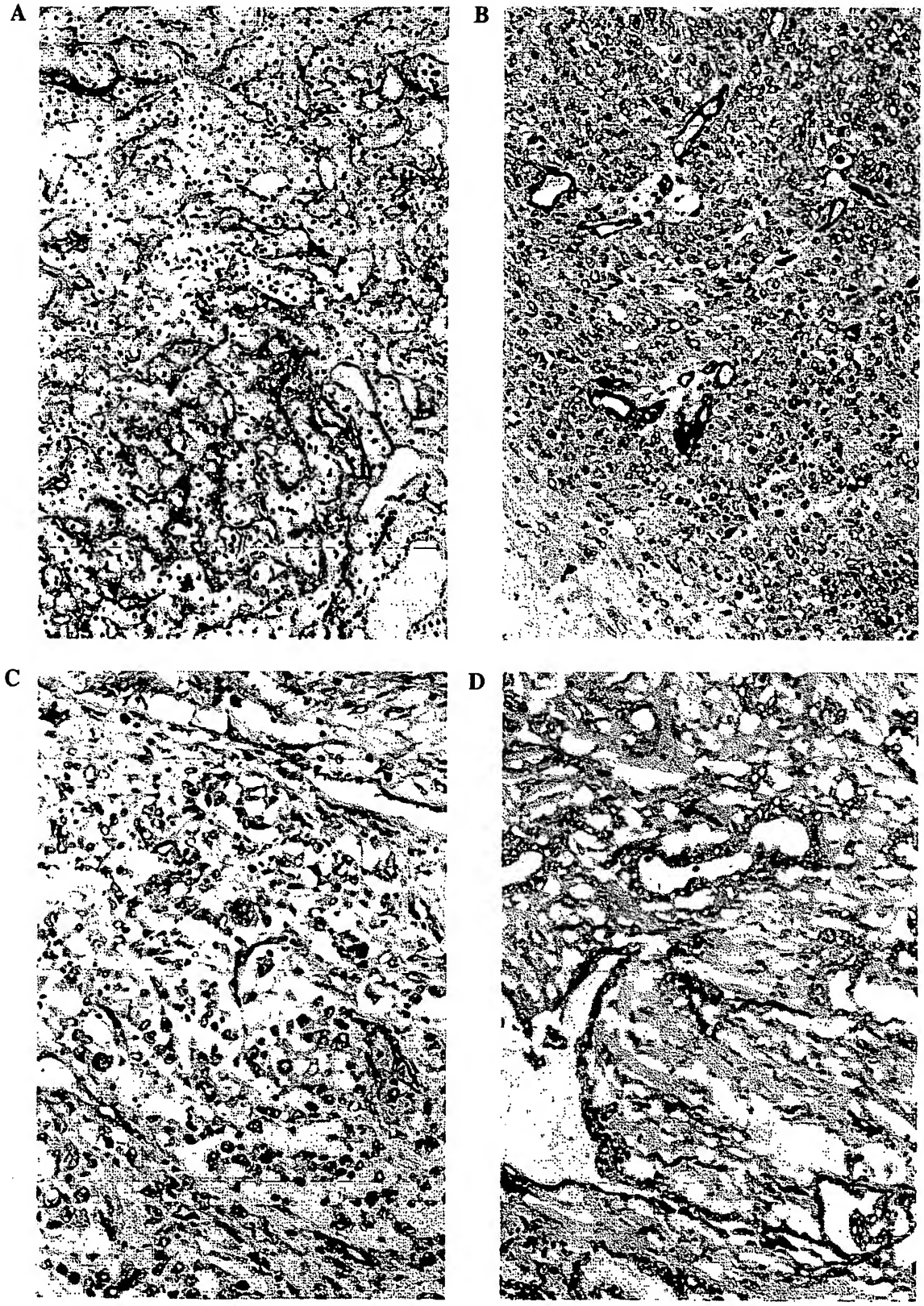

FIG. 3. Tumor-associated neovasculature expresses PSMA. (A) Conventional (clear cell) renal cell carcinoma. (B) Lung cancer. (C) Soft-tissue sarcoma. (D) Pancreatic cancer.

pulsed by these peptides. A small number of patients (9/33) had a partial response, with greater than 50% reductions in serum PSA.[31]

Combinations of anti-PSMA antibodies or antibodies to other previously described targets such as GM2, KSA, TF, or others yet to be identified offer the potential for more specific therapy for prostate cancer.[32,33] However, the sense of encouragement arising from results with novel therapies must be tempered by the fact that certain nonprostatic tissues also bind these antibodies. In addition, attaching various isotopes or drugs to the anti-PSMA antibody may make them less able to enter prostate cancer cells.

These concerns are real but are not absolutely inhibitory. No cancer-specific antigen has yet been found, and the lack of absolute tissue or cancer specificity has not hindered trials of current therapeutic mAbs.[34,35] In addition, the mAbs possessing external domain-binding activity will likely prove more effective than 7E11, because they bind viable cells and are in fact internalized.[36] Because they are internalized, these external domain-binding antibodies offer an even more attractive approach to focusing the delivery of tumor toxins or drugs.

Therapeutic options using PSMA as a target extend beyond the treatment of prostate cancer. The possibilities for treatment of nonprostatic malignancies by utilizing the tumor-associated neovasculature expression of PSMA are intriguing and exciting. All cancers require angiogenesis to thrive and to metastasize, and it is this neovasculature that expresses PSMA, not the vasculature in normal tissue. The presence of a target in the endothelial cells of vessels avoids the requirement for an antibody-based treatment to traverse the vasculature and stroma to enter the cancerous cell. With PSMA expression in a wide variety of tumor-associated neovasculature, targeting strategies utilizing anti-PSMA mAbs may be effective.

CONCLUSIONS

With its consistent expression in prostate cancer specimens, regardless of hormonal treatment, PSMA is an excellent target for both diagnostic and therapeutic modalities in prostate cancer. At present, the 7E11 mAb is being utilized for immunoscintigraphy. Research continues on various treatment strategies that utilize PSMA; and new antibodies that bind the external domain of PSMA, and thus may be more effective, are being developed rapidly.

With recent findings, the possible therapeutic functions of these anti-PSMA antibodies extend beyond prostate cancer. The clear difference in PSMA expression between vessels associated with tumors and vessels of normal tissue is significant and makes PSMA a unique angiogenic target. The endothelial cell targets examined, such as VEGF receptors, CD31, and $\alpha_v\beta_3$ integrin, are found in normal vessels and are upregulated in cancer. Theoretically, then, treatment using these proteins as targets may be hazardous to normal vasculature. Thus far, however, PSMA has not been found in normal vessels in benign or noncancerous tissue, and strategies utilizing PSMA mAbs thus would avoid the risk of damage to normal blood vessels. The important role of angiogenesis in the formation and spread of malignancy is well documented, and antiangiogenic strategies have had promising results with little morbidity.[37] Thus, these anti-PSMA mAbs represent a novel antiangiogenic targeting tool for future radioimaging and treatment options, not only for prostate cancer, but also for other malignant solid tumors.

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Thank you.

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Review

Detection of Prostate Cancer and Predicting Progression: Current and Future Diagnostic Markers

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ABSTRACT

Carcinoma of the prostate is the second leading cause of male cancer-related death in the United States. Better indicators of prostate cancer presence and progression are needed to avoid unnecessary treatment, predict disease course, and develop more effective therapy. Numerous molecular markers have been described in human serum, urine, seminal fluid, and histological specimens that exhibit varying capacities to detect prostate cancer and predict disease course. However, to date, few of these markers have been adequately validated for clinical use. The purpose of this review is to examine the current status of these markers in prostate cancer and to assess the diagnostic potential for future markers from identified genes and molecules that display loss, mutation, or alteration in expression between tumor and normal prostate tissues. In this review we cite 91 molecular markers that display some level of correlation with prostate cancer presence, disease progression, cancer recurrence, prediction of response to therapy, and/or disease-free survival. We suggest criteria to consider when selecting a marker for further development as a clinical tool and discuss five examples of markers (chromogranin A, glutathione *S*-transferase π 1, prostate stem cell antigen, prostate-specific membrane antigen, and telomerase reverse transcriptase) that fulfill some of these criteria. Finally, we discuss how to conduct evaluations of candidate prostate cancer markers and some of the issues involved in the validation process.

INTRODUCTION

Carcinoma of the prostate is the second leading cause of male cancer-related death in the United States, and it is estimated that in 2003 there were approximately 220,900 new cases and 28,900 deaths from this disease (1). Since the introduction of serum prostate-specific antigen (PSA) screening of asymptomatic populations, prostate cancer incidence rates have increased dramatically, as has the number of men undergoing radical prostatectomy and radiation therapy for this disease (1, 2). However, false positives for PSA continue to be a significant problem resulting in unnecessary biopsies, and the value of broad-based PSA testing with regard to predicting surgical cures has recently come into question (3).

Currently, there are no markers that differentiate clinically relevant from clinically benign disease. Better indicators of prostate cancer presence and progression are needed to avoid unnecessary treatment, predict disease course, and develop more effective therapy. A variety of putative prostate cancer markers have been described in human serum, urine, seminal fluid, and histological specimens. These markers exhibit varying capacities to detect prostate cancer and to predict disease course. These markers are distinct from chromosomal aberrations that have been associated with prostate cancer, which will not be dealt with here (4).

The purpose of this review is to examine the current status of markers in prostate cancer and to assess the diagnostic potential for future markers from identified genes and molecules that display loss, mutation, or alteration in expression between tumor and normal prostate tissues. To date, few of these markers have achieved widespread clinical utility. If we are to improve on the treatment of prostate cancer in the 21st century, we must identify and develop markers that are more clinically informative for this disease and that will allow risk-based individualization of therapy.

A BRIEF HISTORY OF PROSTATE CANCER DIAGNOSTICS

The first documented case of prostate cancer was reported by Langstaff in 1817 (5). One hundred eighteen years later, in 1935, prostatic acid phosphatase (PAP) levels were identified in the ejaculate of men, thus linking this enzyme to the prostate (6). Subsequent studies showed high PAP concentrations in primary and metastatic prostate cancer tissues and in human serum, making it the first candidate marker for the diagnosis of prostate cancer (7, 8). Reductions in serum PAP levels were found to occur in response to antiandrogen therapy, whereas increasing serum levels were associated with treatment failure and relapse (9, 10). However, whereas serum PAP levels were elevated in a significant number of men with metastatic disease (8), fewer than 20% of men with localized prostate cancer exhibited abnormal enzyme levels (11, 12). Meticulous sample collection and preparation were required because both platelets and leukocytes are contaminating sources of acid phosphatases (13) and because PAP activity is rapidly lost at room temperature (14). Development of a radioimmune assay for PAP in 1975 provided some improvement in test sensitivity (15), but the sensitivity levels were still inadequate for detection of early-stage disease. Therefore, it was clear that a more sensitive and robust indicator

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of disease presence would be required to detect prostate cancer in its earlier stages, when cure is more likely.

PSA is a kallekrein-like serine protease that was first described in 1971 (16). PSA is secreted from prostate epithelial cells and encoded by an androgen-responsive gene located on chromosome 19q13.3–13.4 (17). The main function of PSA is to liquefy human semen through its proteolytic action (18). PSA was initially thought to be a prostate-specific protein; however, subsequent investigations demonstrated that PSA is secreted in small quantities from a number of other normal male tissues and even some female tissues (19, 20). PSA was first detected in the serum of prostate cancer patients in 1980 (19), and a normal PSA serum concentration limit of 4 ng/ml for men was subsequently established (20). A serum level above 4 ng/ml was taken as an indicator of the possible presence of prostate cancer and served as the trigger for further clinical evaluation. Eventually, a number of studies enrolling large numbers of men over the age of 50 years suggested that quantitation of serum PSA was a useful diagnostic tool for detecting the presence of prostate cancer, particularly when combined with digital rectal examination (21–24). However, other studies have called into question the sensitivity and specificity of the PSA test (25–28). One problem is that serum PSA levels can be elevated as a result of conditions other than prostate cancer, such as benign prostatic hypertrophy (BPH) and prostatitis. As a result, false positives are a significant problem for the PSA test and can lead to unnecessary biopsies and other interventions. Of greater concern, 20–30% of men with prostate cancer have serum PSA levels in the normal range, resulting in undiagnosed disease (22–24). A recent study by Stamey *et al.* (3) has concluded that preoperative serum PSA levels do not correlate with cancer volume or the Gleason grade of radical prostatectomy specimens. This study also showed a poor correlation between preoperative serum PSA levels in the 2–9 ng/ml range and prostate cancer cure rates. Despite the drawbacks and criticisms cited here, PSA is currently the best clinical marker available for prostate cancer and the only one approved by the United States Food and Drug Administration for both posttreatment monitoring of disease recurrence and, when combined with digital rectal examination, evaluation of asymptomatic men (29, 30).

GENES AND PROTEINS CORRELATING WITH PROSTATE CANCER PRESENCE AND PROGRESSION

At the direction of the United States Congress and spearheaded by the National Cancer Institute, support for basic and translational research in prostate cancer has expanded dramatically since 1992. This has resulted in an avalanche of data, much of it attempting to correlate various gene and protein markers with prostate cancer presence, progression, or disease-free survival. Some of these markers have also been proposed as potential therapeutic targets for prostate cancer treatment. However, to date, none of these candidate markers has been adequately validated for clinical use, and no replacement for PSA is visible on the scientific horizon.

Table 1 provides information on 91 genes and their encoded proteins, all of which have a potential role in prostate carcinogenesis and/or progression. All display some level of correlation with one or more of the following factors: presence of prostate cancer, disease progression, cancer recurrence, prediction of response to therapy, or disease-free survival. Information on these markers was accumulated through literature searches using PubMed and from the GeneCards database of human genes, their products, and their involvement in diseases (31). Evidence for the association of a specific marker with human prostate cancer range from a single publication, as in the case of UROC 28, to thousands of publications, as in the case of PSA. In light of the rapid pace of new marker discovery through the use of comprehensive DNA expression analysis and proteomics, there are no doubt candidate markers missing from this list. However, we have made Table 1 as current as possible, and we hope that it will serve as a resource for the prostate cancer research community. In Table 1, we present 89 proteins (the transcripts for DD3 and PCGEM1 do not contain open reading frames) that have been correlated with some aspect of prostate cancer presence or progression in one or more studies. They are listed in alphabetical order and categorized according to their subcellular location: nucleus; cytoplasm; plasma membrane; cytoskeleton; mitochondria; microsomal membrane; endoplasmic reticulum; lysosome; or secreted. The latest information on chromosomal location and molecular weight is included, along with the most common biochemical function of the protein and its major cellular function. In cases in which the biochemical and/or cellular functions of the proteins remain to be determined, the word "unknown" appears in the appropriate column. Alterations for some of these markers, such as p53 and telomerase reverse transcriptase (TERT), can be associated with specific pathways that clearly impact tumor growth and progression; for others, such as DD3 and PC-1, the causal connection is less clear. This is the case for many of the markers presented in Table 1. Whereas an informative marker need not have a specific function in disease progression (PSA is a good example), such a function is useful for understanding the molecular mechanisms of tumor progression and for developing targeted therapeutic interventions.

POTENTIAL FOR DIAGNOSTIC USE

The markers displayed in Table 1 represent a wide array of biochemical and cellular functions. These functions include those of transcription factor, protease, kinase, phosphatase, protease inhibitor, cyclin-dependent kinase inhibitor, cytokine, reverse transcriptase, racemase, reductase, synthase, hydrolase, RNase, molecular chaperone, nuclear matrix, membrane scaffolding, and an assortment of other binding and permeability control proteins. There are also 9 proteins with unknown or poorly defined biochemical functions.

The question is, which of these 91 molecules, if any, are candidates for advancement "from the laboratory bench to the clinic?" This is a broad question that really has a number of parts. First, on what basis do we select from this growing list of candidate diagnostic markers those to pursue in large-scale validation studies designed to prove clinical usefulness? Second, how should these validation studies be conducted and evaluated? Third, what evidence is required to demonstrate that a new marker provides a defined "value added" to the existing methods of prostate cancer detection and for determining the likeli-

hood of disease progression and recurrence and/or response to a given therapy? Fourth, how can we successfully standardize a putative clinical assay to ensure accurate, consistent results across a broad spectrum of research and/or clinical laboratories? This review will focus on the first two questions because addressing them is a prerequisite for moving on to questions 3 and 4.

MARKER SELECTION CRITERIA

What criteria do we consider when selecting one or more of these potential markers for further development as a clinical tool, and will any of the 89 proteins and 2 transcripts presented in Table 1 satisfy these criteria? The most important item regarding the selection of a candidate marker is the quality of scientific and clinical data supporting its potential utility. These include scientific studies relating the functional role of the gene/protein to the biology of the disease and clinical data linking the candidate marker with disease presence, alterations in stage, response to therapy, and/or overall survival. The marker should be measurable by a robust, reproducible, widely available assay that provides useful information that is readily interpretable by the clinician. The ideal candidate for an early detection or disease monitoring marker would be one that is prostate specific; detectable in an easily accessible biological fluid such as human serum, urine, or prostatic fluid; and able to distinguish between normal, BPH, prostatic intraepithelial neoplasia, and cancerous prostate tissues. In addition, the marker should have sufficiently convincing clinical correlation data from several different laboratories before it is brought forward for large-scale evaluation. Whereas it is unreasonable to expect that any single potential diagnostic marker by itself will be able to fulfill all of these criteria, which molecules in Table 1 are the most promising candidates to become clinically useful diagnostic or monitoring markers, and on what basis should we make our selection?

For a marker to be useful for diagnosis and monitoring of disease, it must be demonstrated that the marker correlates with an outcome of interest, such as disease progression, recurrence, or survival. Analyses should be multivariate and should show that the marker(s) predict the outcome of interest independently of the usually available characteristics, such as stage or grade. These assessments should be conducted on a set of cases with adequate outcome data and a sufficient number of events to allow statistical significance to be evaluated. The introduction of tissue microarrays promises to streamline this process considerably.

In the absence of these supportive data, even the most promising marker will not convince either the clinical or pharmaceutical communities that it is worth substantial investment for further evaluation. Based on an analysis of published reports regarding the candidate markers in Table 1, there are five markers that appear to have a significant volume of convincing supportive data, both biological and clinical, associated with them. There are several other candidate markers that have significant supportive data; however, for the purpose of this review, we will discuss these five as examples: chromogranin A (GRN-A); glutathione *S*-transferase π 1 (GSTP1); prostate stem cell antigen (PSCA); prostate-specific membrane antigen (PSMA); and TERT. Their selection in no way diminishes the potential importance of the other markers in Table 1. Each of the proteins listed in the table has different strengths and weaknesses as a clinical prostate cancer marker, and no doubt proteins other than the ones we focus on here will be brought forward for clinical evaluation in the future.

CANDIDATE MARKERS

To choose a marker for diagnosis or prognosis of disease course to bring forward for large-scale clinical evaluation, it should fulfill several criteria. First, there should be a biological or therapeutic rationale for choosing the marker, or at least a consistent association with disease presence, disease characteristics such as stage, or disease aggressiveness. Second, there should be an assessment of the strength of marker association with disease outcome. Third, the marker should be assessed as an independent predictor in a multivariate analysis. The merits and disadvantages of each of the five candidate markers we have selected for scrutiny within the context of the above criteria are discussed below.

GRN-A. GRN-A is a member of the granin family of proteins and acts as a prohormone, which, after proteolytic processing, results in the generation of multiple peptides with biological activity (32). GRN-A is stored in the dense core secretory granules of most endocrine and neuroendocrine cells and is a marker of neuroendocrine differentiation (33). Whereas serum levels of GRN-A do not accurately distinguish BPH from prostate cancer very well, they do correlate with tumor stage and grade. In addition, this marker has the capability to detect neuroendocrine cells and thus has the potential to identify androgen-independent disease. Serum GRN-A levels exhibit a well-documented rise in late-stage disease and demonstrate a wide prevalence range of 32–71%, depending on the study cited (34–43). Studies involving GRN-A have been conducted in human serum using radioimmune assay or ELISA and in tissue using immunohistochemistry (IHC). Elevated serum levels of GRN-A appear to predict poor prognosis in cases of androgen-independent prostate cancer after endocrine therapy and may be an intermediate marker of early progression for this form of the disease and a possible predictor of early death (44, 45). One study used multivariate analysis to demonstrate a significant association between GRN-A positivity and death from prostate cancer (45). Prostate neuroendocrine cells do not contain androgen receptors or produce PSA; thus hormone-refractory disease could be detected earlier in a population of men with apparently normal PSA levels than is currently possible. Whereas GRN-A does not appear to be prognostic of disease recurrence after radical prostatectomy or radiation therapy (46, 47), one report links elevated serum levels to response to estramustine therapy (48). Two significant weakness of GRN-A as a marker are that not all prostate tumors contain neuroendocrine cells and that GRN-A is unable to detect very early stage disease. However, previous studies suggest that GRN-A is able to monitor treatment success, predict disease outcome, and predict prognosis in androgen-independent prostate cancer. There are statistically significant data suggesting that when combined with PSA, elevated GRN-A levels may effectively predict a poor prognosis after endocrine therapy (49). Taken together, this evidence

Table 1 Potential prostate cancer markers

Marker	Chromosome locus	M_r[a]	Subcellular location	Biochemical function	Biological/cellular function
A2M	12p13.3-12.3	163	Secreted	Protease inhibitor	Protein carrier
Akt-1	14q32.32	56	Nucleus/cytoplasm	Protein kinase	Apoptotic inhibition
AMACR	5p13.2-q11	42	Mitochondria/peroxisome	Racemase	Stereoisomerization
Annexin 2	1q21	11	Plasma membrane	Calcium and lipid binding	Membrane trafficking
Bax	19q13.3-.4	21	Cytoplasm/membrane	Bcl-2 binding	Apoptosis
Bcl-2	18q21.3	26	Mitochondrial membrane	Membrane permeability	Apoptosis
Cadherin-1	16q22.1	97	Plasma membrane	Catenin/integrin binding	Cell adhesion
Caspase 8	2q33-34	55	Cytoplasm	Protease	Apoptosis
Catenin	5q31	100	Cytoskeleton	Cadherin binding	Cell adhesion
Cav-1	7q31.1	20	Plasma membrane	Scaffolding	Endocytosis/signaling
CD34	1q32	41	Plasma membrane	Scaffolding	Cell adhesion
CD44	11p13	82	Plasma membrane	Hyaluronate binding	Cell adhesion
Clar1	19q13.3-.4	34	Nucleus	SH3 binding	Unknown
Cox-2	1q25.2-.3	69	Microsomal membrane	Prostaglandin synthase	Inflammatory response
CTSB	8p23.1	38	Lysosome	Protease	Protein turnover
Cyclin D1	11q13	34	Nucleus	CDK[b] regulation	Cell cycle
DD3	9q21-22	0	Nucleus/cytoplasm	Noncoding	Unknown
DRG-1	22q12.2	43	Cytoplasm	GTP binding	Cell growth/differentiation
EGFR	7p12	134	Plasma membrane	EGF binding	Signaling
EphA2	1p36	11	Plasma membrane	Tyrosine kinase	Signaling
ERGL	15q22-23	57	Plasma membrane	Lectin/mannose binding	Unknown
ETK/BMK	Xp22.2	78	Cytoplasm	Tyrosine kinase	Signaling
EZH2	7q36.1	85	Nucleus	Transcription repressor	Homeotic gene regulation
Fas	11q13.3	23	Plasma membrane	Caspase recruitment	Apoptosis
GDEP	4q21.1	4[c]	Unknown	Unknown	Unknown
GRN-A	14q32	50	Secretory granules	Statin	Endocrine function
GRP78	9q33.3	72	Endoplasmic reticulum	Multimeric protein assembly	Cell stress response
GSTP1	11q13	23	Cytoplasm	Glutathione reduction	DNA protection
Hepsin	19q11-13.2	45	Plasma membrane	Serine protease	Cell growth/morphology
Her-2/Neu	17q21.1	138	Plasma membrane	Tyrosine kinase	Signaling
HSP27	7q11.23	23	Cytoplasm	Chaperone	Cell stress response
HSP70	6p21.3	70	Cytoplasm	Chaperone	Cell stress response
HSP90	11q13	63	Cytoplasm	Chaperone	Cell stress response
Id-1	20q11.1	16	Nucleus	Transcription factor	Differentiation regulator
IGF-1	12q22-23	17	Secreted	IGFR ligand	Signaling
IGF-2	11p15.5	20	Secreted	IGFR ligand	Signaling
IGFBP-2	2q33-34	35	Secreted	IGF binding	Signaling
IGFBP-3	7p13-12	32	Secreted	IGF binding	Signaling/apoptosis
IL-6	7p15.3	24	Secreted	Cytokine	B-cell differentiation
IL-8	4q13.3	11	Secreted	Cytokine	Neutrophil activation
KAI1	11p11.2	30	Plasma membrane	CD4/CD8 binding	Signaling
Ki67	10q25-ter	358	Nucleus	Nuclear matrix associated	Cell proliferation
KLF6	10p15	32	Nucleus	Transcription factor	B-cell development
KLK2	19q13.41	29	Secreted	Protease	Met-Lys/Ser-Arg cleavage
Maspin	18q21.3	42	Extracellular	Protease inhibitor	Cell invasion suppressor
MSR1	8p22	50	Plasma membrane	LDL receptor	Endocytosis
MXI1	10q25.2	26	Nucleus	Transcription factor	Myc suppression
MYC	8q24.12-.13	49	Nucleus	Transcription factor	Cell proliferation
NF-kappaB	10q24	97	Nucleus	Transcription factor	Immune response
NKX3.1	8p21	26	Nucleus	Transcription factor	Cell proliferation
OPN	4q22.1	35	Secreted	Integrin binding	Cell-matrix interaction
p16	9p21	17	Nucleus	CDK inhibitor	Cell cycle
p21	6p21.2	18	Nucleus	CDK inhibitor	Cell cycle
p27	12p13.1-12	22	Nucleus	CDK inhibitor	Cell cycle
p53	17p13.1	44	Nucleus	Transcription factor	Growth arrest/apoptosis
PAP	3q21-23	45	Secreted	Tyrosine phosphatase	Signaling
PART-1	5q12.1	7	Nucleus/cytoplasm	Unknown	Unknown
PATE	11q24.2	14	Plasma membrane	Unknown	Unknown
PC-1	5q35	32	Nucleus	RNA binding	Ribosome transport
PCGEM1	2q32	0	Nucleus/cytoplasm	Noncoding	Cell proliferation/survival
PCTA-1	1q42-43	36	Cytoplasm	Unknown	Cell adhesion
PDEF	6p21.31	38	Nucleus	Transcription factor	PSA promoter binding
PI3K p85	5q12-13	84	Cytoplasm	Lipid kinase	Signaling
PI3K p110	1p36.2	120	Cytoplasm	Lipid kinase	Signaling
PIM-1	6p21.2	36	Cytoplasm	Protein kinase	Cell differentiation/survival
PMEPA-1	20q13.31-33	32	Plasma membrane	NEDD4 binding	Growth regulation
PRAC	17q21.3	6	Nucleus	Choline/ethanolamine kinase	Unknown
Prostase	19q13.3-.4	27	Secreted	Serine protease	ECM degradation
Prostasin	16p11.2	36	Plasma membrane	Serine protease	Cell invasion suppressor

Table 1 Continued

Marker	Chromosome locus	M_r[a]	Subcellular location	Biochemical function	Biological/cellular function
Prostein	1q32.1	60[a]	Plasma membrane	Unknown	Unknown
PSA	19q13.3-.4	71	Secreted	Protease	Semen liquification
PSCA	8q24.2	13	Plasma membrane	Unknown	Unknown
PSDR1	14q23-24.3	35[a]	Nucleus/cytoplasm	Dehydrogenase reductase	Steroid metabolism
PSGR	11p15	35	Plasma membrane	Odorant receptor	Unknown
PSMA	11p11.2	84	Plasma membrane	Folate hydrolase	Cell stress response
PSP94	10q11.23	13	Secreted	FSH inhibitor	Growth inhibition
PTEN	10q23.3	47	Cytoplasm	Protein/lipid phopatase	Signaling
RASSF1	3p21.31	33	Cytoplasm	Ras binding	Signaling
RB1	13q14.2	106	Nucleus	E2F-1 inactivation	Cell cycle
RNAseL	1q25.3	84	Cytoplasm/mitochondria	RNAse	Viral resistance
RTVP-1	12q21.1	29	Plasma membrane	Unknown	Immune response/apoptosis
ST7	7q31.2	60/85	Plasma membrane	Unknown	Cell proliferation
STEAP	7q21.23	40	Plasma membrane	Unknown	Unknown
TERT	5p15.33	127	Nucleus	Reverse transcriptase	Telomere synthesis
TIMP 1	Xp11.3-.23	23	Secreted	Protease inhibitor	Cell adhesion
TIMP 2	17q25	24	Secreted	Protease inhibitor	Cell adhesion
TMPRSS2	21q22.3	54	Plasma membrane	Serine protease	Unknown
TRPM2	8p21-12	52	Plasma membrane	Calcium channel	Ion flux
Trp-p8	2q37.1	120	Plasma membrane	Calcium channel	Ion flux
UROC28	6q23.3	17	Nucleus/cytoplasm	Choline/ethanolamine kinase	Unknown
VEGF	6p12	27	Secreted	VEGFR binding	Angiogenesis

[a] Molecular weight (in thousands) estimated from amino acid data.

[b] CDK, cyclin-dependent kinase; EGF, epidermal growth factor; IGFR, insulin-like growth factor receptor; IGF, insulin-like growth factor; LDL, low-density lipoprotein; ECM, extracellular matrix; FSH, follicle-stimulating hormone; VEGFR, vascular endothelial growth factor receptor.

[c] Data for Table 1 resourced from GeneCards database, Weizmann Institute of Science (31).

makes GRN-A a good candidate for further clinical evaluation as a prognostic and/or treatment marker for prostate cancer.

GSTP1. GSTP1 is a member of a large family of glutathione transferases that function to protect cells from oxidative insult (50); thus, the biological rationale for selecting this marker is its role in preventing damage to cells by neutralizing free radicals. This marker is also unique in its capacity to provide a facile methylation-based detection method for an important epigenetic phenomenon. GSTP1 has been extensively studied in prostate cancer, and its reduced expression, due predominantly to promotor hypermethylation, represents the most common epigenetic alteration associated with this disease. One study has shown that in prostate cancer cells, methylation of the *GSTP1* gene is not confined to the promoter but is extensive throughout the CpG islands (51). Several studies have shown a high sensitivity for this marker to detect the presence of both prostatic intraepithelial neoplasia and prostate cancer, an ability to distinguish these from BPH, and a prevalence of methylation in the range of 60–80% in prostate cancer (51–61). In addition, several *GSTP1* polymorphisms have shown a correlation with increased risk of disease development, although data regarding this ability are conflicting (62–67). Strengths of GSTP1 as a clinical marker are the ability to quantitate the methylation status of the *GSTP1* gene in biopsy/prostatectomy tissues and in cells derived from serum, urine, and seminal plasma and its high prevalence in this disease. Recent studies using quantitative real-time methylation-sensitive PCR demonstrate that *GSTP1* methylation could be a sensitive marker for prostate cancer in men with clinically localized disease (51). In addition, there is no correlation between *GSTP1* methylation status and PSA levels, making GSTP1 a potential early and independent marker for the disease. The ability of *GSTP1* hypermethylation to distinguish between BPH and prostate cancer is well documented, and one recent study correlated methylation status with poor prognosis in 101 patients diagnosed with prostate cancer (68). However, whereas these results are statistically significant, they were not tested by multivariate analysis. Reversal of *GSTP1* CpG island hypermethylation and gene reactivation in LNCaP prostate carcinoma cells can be achieved by procainamide treatment; however, no effect on tumor cell growth was observed in these studies (69). The strengths of *GSTP1* methylation status, as cited above, and the possible availability in the near future of drugs that can reverse hypermethylation make it a good candidate for further evaluation as an early detection marker. If successfully validated, *GSTP1* methylation testing of cells derived from serum and urine samples may have clinical usefulness for both early detection of prostate cancer and posttreatment monitoring of disease.

PSCA. PSCA is a glycosylphosphatidylinositol-anchored cell surface antigen that is found predominantly in prostate and may play a role in stem cell functions such as proliferation or signal transduction (70). Whereas the biological role of PSCA in prostate cancer is unclear, the marker is expressed predominantly in the prostate and has potential as a therapeutic target. Other strengths of PSCA as a prostate cancer marker include elevated PSCA expression levels in the majority of prostate cancers and a correlation between this elevation and higher Gleason grade and more advanced tumor stage (71–74). Published studies also show a high correlation (64–94%) between increased PSCA expression and the presence of prostate cancer, with protein expression localized to both the basal and secretory cells (71–75). PSCA has been assayed by a variety of methods, including *in situ* hybridization, quantitative reverse transcription-PCR, and IHC, demonstrating a prevalence of 48–94% for

prostate cancer (71, 72, 76). One IHC study demonstrated an association between increased PSCA expression and higher Gleason score, more advanced tumor stage, and progression to androgen-independent prostate cancer (72). However, extensive multivariate analysis to confirm these findings has yet to be performed. PSCA expression is maintained in androgen-independent prostate cancer, and PSCA is highly expressed in metastatic disease (71–76). Whereas most of the studies performed to date have been on prostate tissue samples, there is at least one report of PSCA detection in peripheral blood (73). Another strength of this marker is its potential as a therapeutic target. Anti-PSCA monoclonal antibodies have been shown to inhibit tumor growth and metastasis formation of human xenografts grown in *scid* mice (76). This opens up the possibility for therapeutic treatment of human prostate cancers using immunotherapeutic regimens (76–78). In addition, PSCA is co-amplified with the tumor progression factor and oncogene c-*myc* in locally advanced prostate cancers, suggesting a role for PSCA in the progression of this disease (74, 79). Three weaknesses of PSCA as a candidate for further development are the limited number of published studies supporting its value as a clinical marker, a need for better quantitation methods, and uncertainty as to whether analysis of PSCA levels adds information to the results of PSA testing. However, based on the available data and the value of PSCA as a therapeutic target, further evaluation of PSCA as a clinical prostate cancer marker should be performed to determine its utility.

PSMA. Discovered in 1987, PSMA is a cell surface membrane protein and one of the most extensively studied prostate cancer markers cited in Table 1 (80). PSMA is a type II integral membrane protein that displays multiple enzymatic activities (81, 82). The protein translocates from the cytosol in normal prostate to the plasma membrane in prostate cancer (83). The exact biological role of PSMA in the disease mechanism is unclear at this time; however, extensive data exist on its utility as a marker and therapeutic target. Numerous studies have shown that PSMA serum levels are elevated in primary prostate cancer and metastatic disease, that PSMA demonstrates a >90% prevalence in the disease, and that levels can be detected in both tumor tissue and serum using several antibodies (84–91). PSMA has been detected in prostate tissues using IHC and Western analysis, in circulating prostate cancer cells by reverse transcription-PCR, and in serum using ELISA assays. One study using Western analysis demonstrated that in postprostatectomy patients, PSMA values are elevated in hormone-refractory tumors, suggesting that PSMA levels may correspond with poor clinical outcome (85). In another study (92), PSMA serum levels were found to increase with age and were significantly elevated in men over 50 years of age. To date, however, increased PSMA serum levels have not been convincingly linked to disease aggressiveness, and perhaps due to tumor differentiation status, some studies have shown that levels actually decrease in advanced disease (93). PSMA protein has also been shown to be up-regulated in prostate cancer patients after androgen deprivation therapy (94). Recent technological advances have allowed for the high-throughput assay of this marker in human serum using a protein chip, mass spectrometry platform (95). That study demonstrated significantly greater PSMA levels in men with prostate cancer than in those with BPH or with no evidence of disease. PSMA is moderately prostate specific and has been investigated as a target for immunotherapy using autologous dendritic cells (96). Efforts are also under way using the PSMA gene promoter to pursue gene therapy strategies by introducing cytotoxic agents into prostate cancer cells (97). A weakness of PSMA as a clinical marker for early diagnosis is that elevated serum levels have been observed in healthy males and females and in the serum of breast cancer patients (98). Another weakness is that serum levels of PSMA have been shown to increase with increasing age, which could be a confounding factor in a disease that most often occurs late in life. However, there is an abundance of data supporting the ability of PSMA to detect the presence of prostate cancer, and new technologies are being developed that allow quantitative high-throughput analysis of biological fluids. This argues in favor of further evaluation of this marker to determine whether or not it has clinical utility for prostate cancer detection or treatment monitoring or as a treatment target.

TERT. The *TERT* gene encodes the reverse transcriptase component of telomerase that maintains the telomeric ends of chromosomes and has been associated with senescence and cancer (99). The TERT component is expressed in cells that exhibit telomerase activity and is undetectable in most benign tissues (100). The biological rationale for selecting TERT is the ability of TERT to confer cellular immortalization, a major step in the process of malignant transformation. Thus, this marker may provide a very sensitive means for detecting infiltrating cancer cells in benign tissue. A significant number of studies have been conducted to evaluate TERT or telomerase activity as a marker for prostate cancer (101–119). Published reports demonstrate that TERT activity levels exhibit a prevalence range of 63–94% for prostate cancer, and activity has been detected in some cases of high-grade prostatic intraepithelial neoplasia (100–111). TERT has been most often assayed by IHC or the telomeric repeat amplification protocol assay. Most studies find the marker consistently absent from normal prostate and the majority of BPH tissues. The highest TERT activity appears to correlate with poorly differentiated disease, and there is some evidence for a correlation with tumor stage and grade and patient mortality and disease recurrence (100, 104, 107–109). Whereas statistical significance has been demonstrated in some of these studies, the correlations have not been tested by multivariate analysis. TERT activity does not correlate with PSA level, making it a potential independent marker for prostate cancer. One study suggests that telomere length in tumor tissues correlates with survival and recurrence in prostate cancer patients (120). However, TERT also displays several weaknesses as a clinical marker for prostate cancer detection. TERT is not prostate specific, and in most studies, assays were conducted in prostate tissues, and thus required biopsy material before marker assay. However, several studies have now successfully used human urine, seminal fluid, and prostatic fluid to detect TERT activity (113, 114, 121). Although TERT activity levels appear to be independent of PSA, the "value added" of TERT for early detection, staging, or prognosis and the overall clinical utility of TERT remain to be fully uncovered. Further evaluation of TERT may reveal a niche for use of TERT as a supplement to PSA testing.

MARKERS IDENTIFIED BY ADVANCED TECHNOLOGIES

Recently, methodologies as diverse as positional cloning, differential display, comprehensive DNA expression analysis, and serum proteomic analysis have provided some very preliminary yet exciting prostate cancer marker candidates. Among these are Hepsin, a serine protease associated with cell growth and morphology (122–124); RNase L, a RNase involved in viral resistance and a candidate for the HPC1 gene (125, 126); ST7, a protein of unknown function (127–129); and EZH2, a homeotic protein that participates in the repression of gene expression (130, 131). In addition, proteomic analysis of serum from prostate cancer patients has shown promise for diagnostic and prognostic use for this disease (132). Candidate markers identified by these new technologies will require confirmation and correlation with disease formation or progression or with patient survival or response to therapy in additional human samples before they can be considered for validation studies.

CLINICAL EVALUATION AND AN EVALUATION PROCESS EXAMPLE

To validate the clinical usefulness of any marker, it is important to first establish what the end point will be. This, in turn, will determine the study population that will be examined. The appropriate statistical design of the study will require information on prevalence and the postulated strength of the association of marker expression with the outcome of interest. These considerations will, in turn, determine both specificity and sensitivity of the marker. In some situations, an appropriate control population may be required to determine the specificity of the marker through the determination of false positive and negative rates. Finally, an appropriate sample collection, preparation, and assay method must be decided on. Multi-institutional clinical studies will also likely require the use of a central laboratory or shared controls and training sets of malignant samples to ensure accuracy and consistency. An example may serve to illustrate a reasonable evaluation process.

Suppose we wish to further evaluate a hypothetical marker, which we will call Optimal Marker in Prostate Carcinoma (OMPC), for clinical utility. Previous studies indicate a correlation between OMPC expression and metastatic disease. The clinical question to be addressed is whether this marker can predict which patients with early-stage disease will eventually develop metastatic disease despite local therapy. To accomplish this, we would want to evaluate a large enough number of cases of early-stage prostate cancer for which there is a minimum of 5 years of clinical follow-up data available to obtain a robust assessment of the strength of association between the marker and outcome. The method of OMPC analysis would be selected based on limit of detection, sources of variability, suitability for the samples that will be available, day-to-day and interobserver variability, cost, scalability, and optimum reagents (133). The procedure for scoring or interpreting the results of the assay will need to be optimized to reduce variability. If cut points are to be used, they should also be developed and tested for robustness, if necessary.

The optimized assay is then performed on a large number of early-stage prostate cancer cases, with the hypothetical result that all patients express the marker, but only 40% express at "high" levels as determined by our cut point. For illustrative purposes, say these high expressers have a 2.5× greater risk of developing metastatic disease after local therapy. Does OMPC predict outcome at least as well as or independently of the other known prognostic factors, Gleason score and PSA? Because all of the patients had early-stage cancers, a multivariate analysis including all of the significant prognostic factors would answer this question. If OMPC remained a strong prognostic factor for development of metastatic disease, with a hazard ratio of at least 2, and was independent of other prognostic factors, we would be more confident of its potential value. However, this would require verification in an independent cohort of patients with early-stage prostate cancer receiving a defined initial local treatment. Using an estimate of 40% high expression prevalence, we can calculate the size of the study necessary to determine whether the marker is associated with a hazard ratio of at least 2, with an 80% power to detect a minimum 2-fold effect on the likelihood of metastatic development (134). Whereas we have here addressed the analysis of a single marker, the strategy outlined would also apply to a genomic or proteomic "profile" as determined by comprehensive molecular analysis.

CONCLUSIONS

The development of novel and clinically relevant markers for prostate cancer diagnosis, prognosis, and prediction is essential to the optimal identification and treatment of this disease. With the advent of DNA expression analysis, tissue microarrays, and proteomic analysis, the list of potential prostate cancer markers grows daily. Sorting through these potential markers and bringing them from the laboratory environment into clinical use at the patient bedside will require a comprehensive pursuit and rigorous analysis. Many of the molecules cited in Table 1 have languished for years in a gray zone between usefulness as a clinical marker for prostate cancer and elimination from further consideration. As a research community, we must devise approaches that will ensure that we realize the next generation of clinically relevant prostate cancer markers.

We have here attempted to provide examples of potential prostate cancer markers that may be of clinical benefit in prostate cancer detection, prognosis, and/or prediction. We have also suggested one possible methodology for the clinical evaluation of these markers. The goal of this effort is not to dictate the optimal markers or the methodologies for their verification, but to provide by example a framework from which the general research community can work toward achieving the goal of bringing new prostate cancer markers forward for clinical use.

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Thank you.

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Prostate-Specific Membrane Antigen (PSMA): Current Benefits and Future Value

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We will review the evolution, benefits, and limitations of PSMA testing in the past, as well as its current and future value. Prostate cancer has been the most frequently diagnosed cancer and the second leading cause of cancer death in men in the United States. It has a wide spectrum of biological behavior between latent (indolent) and progressive (aggressive). Further identification of prostate-specific membrane antigen (PSMA) as a prognostic proliferation marker may enhance our understanding of the types of prostate cancer. A review of PSMA testing in the past as well as currently was conducted. Studies were reviewed that deal with detection of PSMA in serum and seminal fluid, reverse transcriptase-polymerase chain reaction (RT-PCR), immunoscintigraphy, and immunohistochemical assays. PSMA is expressed primarily in benign and cancerous prostatic epithelial cells. It is up-regulated in hormone resistant states, and in metastatic situations or other clinical situations where there is tumor recurrence or extension. Based on current results, PSMA detected in the serum by western blotting can assist in the identification, staging, and monitoring of metastatic prostate cancer. In addition, PSMA shows a promising role in directed imaging and therapy of recurrent or metastatic disease. ***Semin. Surg. Oncol. 18:10–16, 2000.***

KEY WORDS: **prostatic neoplasms; adenocarcinoma; biological tumor markers; prostate-specific antigen; western blotting; survival rate; incidence; monoclonal antibodies; radioimmunodetection; indium radioisotopes; reverse transcriptase-polymerase chain reaction; neoplasm metastasis; neoplasm invasiveness; neoplasm circulating cells; immunohistochemistry; human chromosomes pair 11; staining; messenger RNA; prostatic hyperplasia; sensitivity and specificity; lymphatic metastasis; predictive value of tests; epitopes; semen; enzyme-linked immunosorbent assay**

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer deaths in men in the United States [1]. According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, the incidence of distant disease has decreased with increased screening, and consequently, mortality rates have decreased in recent years. However, prostate carcinoma accounted for about 38% of all deaths of men aged 50 years and older; men older than 69 years had a greater chance of death than men in the age range of 50 to 69 years [2, 3]. After diagnosis with prostatic carcinoma, death occurred within 5 years in about 61% of patients and within 10 years in about 88%. SEER program analysis suggested that one-third of patients who are diagnosed fall into the category of those for whom cure is necessary but may not be possible (patients with primary extraprostatic spread or failure after prostate cancer treatment) [2, 3]. These patients ultimately need considerable hospital care and palliative treatments before they finally die of, or with, prostate cancer [4]. For such patients we need additional markers that are not influenced by hormonal therapy and/or tumor dedifferentiation. Prostate-specific antigen (PSA) alone might not reflect the pattern of growth and response to treatment and additional markers like prostate-specific membrane antigen (PSMA) might be warranted for patients with advanced disease [5–8].

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As a serum marker, PSMA has been used in diagnosis of non-localized prostate cancer [8]. PSMA peptides also have been employed as part of a cancer vaccine therapy [9]. To date, the most widely used diagnostic application of PSMA is in the field of radio-immunoscintigraphy. The ^{111}Indium-labeled monoclonal antibody (Mab) 7E11-C5, which recognizes PSMA on the prostatic cell surface, is employed as CYT-356 or ProstaScint® [10, 11]. This radiolabeled Mab can be infused intravenously and provides a means for radio-immunoscintigraphy of extraprostatic spread of the disease [10, 11]. The molecular detection of PSMA, utilizing the reverse transcriptase-polymerase chain reaction (RT-PCR) technique, also allowed for identification of metastatic prostate cancer cells (or prostate-like cells) in the general circulation of most patients with advanced disease [12]. Immunohistochemical staining showed that PSMA expression was related to tumor grading, and that PSMA was more highly expressed than PSA in poorly differentiated primary or secondary prostate cancer lesions [13].

We will review the evolution, benefits, and limitations of PSMA testing in the past, as well as its current and future value. It is hoped that clinical applications of PSMA will enhance our understanding and management of non-localized prostate cancer and help in differentiating latent from progressive variants of the disease.

PSMA DISCOVERY AND EXPRESSION

In 1987, Horoszewicz and colleagues originally defined PSMA as recognized by 7E11-C5.3 Mab. 7E11-C5.3 is a murine immunoglobulin G (IgG_1) Mab derived after immunization of mice with a purified fractions of cell membrane isolated from human prostate cancer LNCaP cells [14]. Immunohistochemical analyses of frozen sections from a variety of normal and malignant human tissues and human cell lines were tested for PSMA expression. Ninety-three percent of 27 specimens from benign and malignant prostates displayed immunoreactivity for PSMA. Staining was restricted to epithelial cells of the prostate, with no staining of stromal components. Prostatic cancer was intensely stained whereas normal and hyperplastic tissue showed weak to moderate staining. Weak reactivity was seen in 2/14 normal human kidney specimens and no staining was observed in 108 specimens from 27 other normal human organs [14].

Further studies from different institutions provided results similar to that of the original report. Immunohistochemical staining for PSMA was also observed in 33/35 primary prostate tumors, in 7/8 specimens of prostate cancer lymph node metastases, and in 8/18 bone metastases [15, 16]. Less intense and non-specific staining was noticed in normal specimens from the brain, salivary glands, sweat glands, renal tubules, cardiac and skeletal muscles and intestines. The variability in the results relating to extraprostatic expression of PSMA may be due to differences in detection methods and experimental protocols [8, 17, 18]. Immunoreactivity for PSMA has been observed in vascular endothelial cells restricted to the cancer region in a variety of tumors, but not in normal vascular endothelium [19]. Recently, immunohistochemical analysis of 184 radical prostatectomy specimens revealed consistent PSMA-staining in all cases [13]. The staining intensity was less in benign epithelium than in adenocarcinoma (mean 69.5% vs. 80.2%). In contrast, immunoreactivity for PSA was higher in benign epithelium than in adenocarcinoma (mean 81.2% vs. 74.2%). Utilizing 7E11.C5 antibody, there was no staining of prostatic stroma, urothelium, or tumor capillary endothelial cells [13]. These studies indicate that PSMA is highly specific for prostate epithelial cells; its increased expression with cancer progression makes it a particularly useful marker for histologic prognostic evaluation.

PSMA CHARACTERISTICS AND FUNCTION

The gene encoding PSMA consists of 19 exons spanning approximately 60-kilo base (kb) of genomic DNA [20]. The coding sequence of PSMA gene is 2.65-kb in length and encodes a 750-amino acid type II transmembrane glycoprotein with a 100 to 120-kilo Dalton (kDa) molecular weight [8, 17]. As shown in Figure 1, PSMA is composed of three structural domains: A 19-amino acid intracellular or N-terminal domain, a 24-amino acid transmembrane domain, and a 707-amino acid extracellular domain. The gene for PSMA has been cloned and fully sequenced and has been localized to the short arm of chromosome 11, probably at 11p11-p12 [20]. It is also suggested that a gene homologous, but not identical, to PSMA exists on the long arm of chromosome 11, i.e., 11q14 [20,21].

PSMA-mRNA is down-regulated by androgens such as 5-α-dihydrotestosterone and is upregulated by growth factors such as basic fibroblast growth factor (bFGF), transforming growth factor-alpha (TGF-α), and epidermal growth factor (EGF). This behavior is consistent with the observed elevated expression of PSMA, either in patients after androgen deprivation therapy or with hormone refractory tumors [22, 23].

The function of PSMA is not clear. Most type II transmembrane proteins are transport proteins or membrane-associated receptors or proteases [21]. Moreover, the high expression of PSMA in prostatic tissues may imply that it has an important physiological function. PSMA may be related to cleaving of the neuropeptidase N-acetylaspartyl glutamate (NAAG) to yield N-acetylaspartate and glutamate. An additional enzymatic activity of PSMA also is a carboxypeptidase that cleaves gamma-glutamyl residues from folate [20]. Increased levels of PSMA in aggressive tumors may imply a role in transformation or invasiveness of prostatic epithelial cells [7,8,17,18].

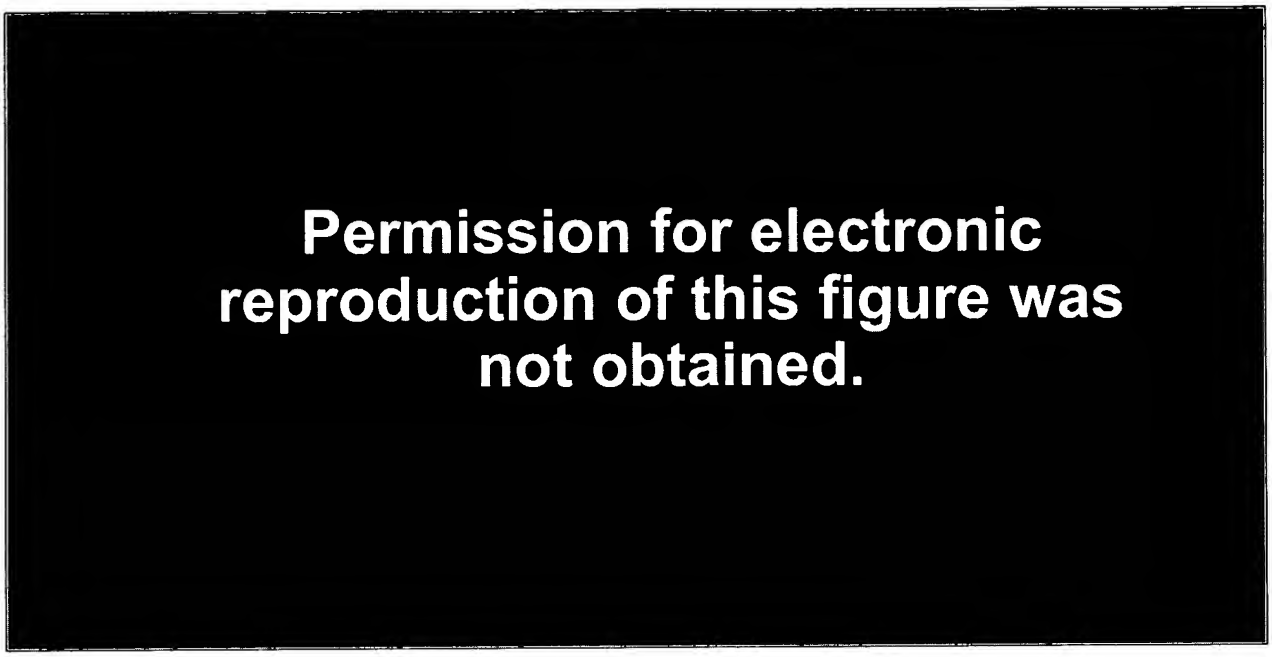

Fig. 1. Diagram representing prostate-specific membrane antigen (PSMA) expressed in the membrane of prostate epithelial cells. PSMA is comprised of a short 19-amino acid intracellular domain, a 24-amino acid transmembrane domain, and a 707-amino acid extracellular domain. PSMA, prostate-specific membrane antigen. [Adapted from [8]: Cancer 83(11) 1998, p. 2259–2269. ©1998 American Cancer Society. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.]

VARIATIONS OF PSMA ANTIGENS AND ANTIBODIES

Su and colleagues examined the expression of PSMA-mRNA in normal prostate using reverse transcriptase-polymerase chain reaction (RT-PCR) and sequencing [24]. They found an alternatively spliced variant designated PSM' which is missing the coding sequence for the first 27-amino acids from the N-terminal of PSMA. This missing region is composed of the intracellular, transmembrane, and a portion of the extracellular domain of PSMA. Published data indicate that PSMA is the dominant form in primary prostate tumors and in LNCaP human prostate cancer cells, whereas normal human prostate expresses more PSM' than PSMA. Specimens of benign prostatic hypertrophy (BPH) show equal expression of both variants [24].

The PSM' protein has recently been purified from LNCaP cells using two immuno-affinity columns in tandem [25]. The 7E11-antibody binds to the first six amino acids from the N-terminal of the full length PSMA protein distributed on the intracellular membrane (this portion is missing in PSM'). Antibody designated PEQ226.5 binds to an epitope common to both PSMA and PSM'. The protein eluted produced a 95 kDa band that was slightly lower than the full-length PSMA. The band was sequenced and coincided with the predicted sequence for PSM' protein minus its first two N-terminal amino acids [25]. Noteworthy is the fact that the latter sequence starts at residue number 60. Residue number 59 is a lysine. This suggests that a trypcin-like cleavage of PSM' may have occurred to cause a loss in these two residues [25].

Recently, Liu et al. [19] and Murphy et al. [26] reported the isolation of new panels of monoclonal antibodies reactive with the extracellular domain of PSMA. The antibodies obtained displayed strong reactivity and specificity for different extracellular epitopes of PSMA. Western blot results also indicated the variable ability of these new antibodies to cross-react with PSM'. The functional and tissue specific properties of each antibody merit additional studies to define their potential clinical usefulness in diagnosis and treatment of non-localized prostate cancer [26]. The Seattle group has obtained several distinctive antibodies that are specific for protein conformational epitopes in the extracellular domain. These antibodies are unreactive with denatured protein but effectively label live prostate cells [26,27].

RADIOIMMUNOSCINTIGRAPHY OF PSMA: PROSTASCINT® SCAN

Primary extraprostatic spread or failure after prostate cancer treatment can occur locally in the prostatic fossa and/or metastasize to regional and/or distant lymphatics and/or in bone. These represent different stages of cancer and have a different prognosis. Although serum PSA may detect treatment failure it does not indicate site(s) of fail-

ure, and can be suppressed by adjuvant hormone therapy [6,28]. Computed tomography (CT) and magnetic resonant imaging (MRI) are dependent on size of lymph node metastases and are not specific for the presence of prostate cancer cells [29]. Guided needle biopsy of prostatic fossa or lymph nodes is a relatively invasive procedure, operator dependent, and subject to inherent sampling errors [30]. A new diagnostic tool, the radiolabeled murine-IgG_1 7E11-C5, also known as CYT-356 or ProstaScint® scan, is an immunoscintigraphy scan that identifies PSMA expression in soft tissues. It has provided means for detecting prostate cancer metastases [10,11]. To date, no other antibody imaging specific for prostate cancer was successful, even when utilizing anti-PSA antibodies [10]. Factors that contributed to the approval of ProstaScint® for imaging prostate cancer include the cell membrane-bound nature of the target antigen (i.e., PSMA) and its high affinity to be expressed in dedifferentiated, metastatic, and hormonally treated prostate cancers [13,17,22]. In addition, few adverse reactions have been reported post-infusion of the antibodies [31]. For instance, testing the serum for human anti-mouse antibody (HAMA) reaction was positive in less than 5% [9,31–36].

Multiple studies have defined the sensitivity and specificity of the ProstaScint® scan in prostate cancer patients who underwent conventional CT or MRI scanning, surgical or needle biopsies [31,33,34]. These individuals may also have exhibited a rising serum PSA after radical prostatectomy [31,33–35,37–41]. Table I illustrates the results of 482 ProstaScint® scans in detecting primary or recurrent prostate cancer that spread locally or regionally to the lymph nodes. These results are better than those of conventional CT scanning: for instance, ProstaScint® has a sensitivity of 75% and an accuracy of 81% whereas CT alone has a sensitivity of 36%—and CT, MRI, and ultrasound have a combined accuracy of only 48% [29,35]. Furthermore, the ProstaScint® scan may be superior to the positron-emission tomography (PET) for identifying recurrent prostate cancer [38]. ProstaScint® also is useful in determining (prior to treatment) if prostate cancer will likely recur or has already spread to other parts of the patient [34,40]. It has been observed that salvage radiotherapy was more likely to lead to a durable complete PSA response in men with prostate cancer who failed radical prostatectomy and had a negative ProstaScint® outside the pelvis as compared with those who had a positive scan [34]. In addition, the ProstaScint® scan was more predictable than clinical staging algorithms (prognostic tables) in predicting lymph node involvement prior to lymphadenectomy in 198 patients with clinical Stage T2-T3 prostate cancer. The positive predictive values of the scan and staging algorithms were 66% and 46%, and areas under ROC curve were 0.71 and 0.6, respectively [40].

At present, it appears that the ProstaScint® scan and serum PSMA test now available may predict patient outcome and describe the extent of cancer more accurately than previously possible [42, 31]. In addition, it is expected that the isolation and characterization of new Mabs specific for extracellular domain of the PSMA may enhance sensitivity of the ProstaScint® scan in the future due to intracellular localization of the binding epitope of the currently used 7E11 antibody [26].

MEASUREMENT OF SERUM PSMA: THEORY AND PRACTICE

Before interpreting the role of serum PSMA measurement in the management of patients with prostate cancer, we need to know the pre-existing limitations. Currently, information about serum PSMA levels in prostate cancer patients are limited and are hampered by two main factors. First, very little is known about how the PSMA molecules are shed into the general circulation and what regulates this process. The exact mechanisms of regulation of PSMA in prostatic cells, as well as the metabolism or yield of PSMA molecules after its release in the blood, are still unclear. The assay used today is a western blot, and does not represent the finest type of assay being developed in our laboratory. A reproducible

TABLE I. Tabulated Results of ProstaScint® Scan Studies

References	No. of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	Overall accuracy (%)
Babaian et al. [33]	19	44	86	50	83	NA	76
Chengazi et al. [37]	35	92	NA	NA	NA	NA	NA
Elgamal et al. [31]	100	89	67	89	NA	NA	89
Haseman et al. [38]	14	86	43	60	75	NA	NA
Hinkle et al. [35]	51	75	86	79	NA	NA	81
Khan et al. [39]	27	94	36	NA	NA	NA	NA
Polascik et al. [40]	198	62	80	66	76	0.71	NA
Ulchaker et al. [41]	38	55	NA	NA	NA	NA	NA
Pooled results	482	74.6	66.3	68.6	78	0.71	82

AUC, area under curve; NA, not available; NPV, negative predictive value; PPV, positive predictive value.

assay with two Mabs is preferred for simple, fast and sensitive measurements. Given these difficulties and the relatively recent discovery of PSMA, there are insufficiently fewer studies on serum PSMA as compared to PSA (fewer than 1% in a MEDLINE search of the literature though December, 1998).

Compared to PSA, PSMA has relatively larger molecular weight and is excreted at lower level in prostatic excretions [5–8, 17, 18, 43, 44].

Today, there are only two research assays available for measurement of serum PSMA levels: The competitive enzyme-linked immunosorbent assay (ELISA) or the western blot technique can be utilized [44–46]. At present, we prefer the latter test. In our studies, western blot quantification was relative and showed the strength of the PSMA-band intensity as revealed from densitometric evaluation of the scanned blots. Nevertheless, higher PSMA levels did correlate with higher pathologic stages but generally not for clinically localized disease [5, 42, 45].

A first-generation competitive ELISA was described by Horoszewicz and colleagues in 1987 [14]–an LNCaP-based assay that utilized Mab 9H10-A4 in addition to 7E11-C5. They demonstrated increased PSMA level in the sera of 47% (20/43) prostate cancer patients, which is three standard deviations above the mean of normal control. They also suggested that patients with a positive ELISA test were more likely to be in cancer progression as compared to those who were negative. Serum PSMA was elevated in only 5% (3/66) nonprostatic cancer patients and in none of 30 normal blood donors or seven BPH patients. Subsequently, Rochon and colleagues confirmed the findings of Horoszewicz et al. using a similar competitive ELISA assay [46]. These observations were conducted on 38 different patients with localized or disseminated disease [44]. Again, the ELISA assay recognized a significant elevation in the serum PSMA, mainly at stage D2, and a rather modest increase in the presence of clinical progression. Sera from BPH patients were not elevated above the normal. The results of PSMA measurement by competitive ELISA suggest that PSMA be of potential use for aggressive or metastatic prostate cancer. The recent isolation of additional Mabs specific for the extracellular domain of PSMA carry a significant potential towards development of a sandwich-sensitive ELISA test for measurement of PSMA [26].

DETECTION OF PSMA IN SEMINAL FLUID

Given the fact that PSMA is a prostate cell surface antigen, it is reasonable to expect its highest yield in semen plasma as compared to blood or other body fluids. Using Western blot analysis, several researchers have demonstrated the presence of PSMA in seminal plasma at very high levels [16,46]. Troyer and colleagues found the most consistent expression of PSMA in seminal plasma obtained from normal donors, demonstrating the 120-kDa band and often an 80-kDa band [16]. Seminal plasma from BPH patients exhibited variable expression of PSMA, ranging from very low to overexpression. The expression of PSMA in prostate cancer patients was comparable to that in normal samples [16].

Using the antibody 7E11-5E and flow cytometry, we have identified prostate cells in seminal fluid [47]. In several cases, the ratio of PSMA: Cytokeratin positive cells was determined, and found to be elevated (mean of 57%) in 11 prostate cancer patients as compared to 12% in 14 normal controls [47]. These data support the hypothesis that seminal PSMA can be useful in diagnosing patients with prostate cancer, however, further research in this area is needed [47].

RT-PCR FOR DETECTION OF PSMA-MRNA

Recent reviews show that RT-PCR is in its earliest stages of development, and should not be summarily dismissed nor should it be used to guide clinical decisions [48–50]. Clinical studies to date have shown that RT-PCR can detect circulating PSA or PSMA-expressing cells in many patients with frank metastases, in a subset with localized prostate cancer, or in negative controls including healthy women and normal healthy men. Too few institutions report a correlation between results of RT-PCR and pathologically staged disease. A negative RT-PCR results does not rule out micrometastases, and at present, the prognosis of a patient with clinically localized disease and a positive RT-PCR is not known [48–50].

It is assumed that cells expressing prostate-specific markers (PSA-mRNA or PSMA-mRNA) are not normally present in blood, bone marrow, or lymph node biopsies. Using PSMA-mRNA as a marker, RT-PCR-assays have been used for detection of prostate cancer micrometastasis in blood. Table II shows a comparison of PSMA and PSA RT-PCR results for groups of patients with metastatic prostate cancer [12,51–55]. The pooled sensitivity of PSMA (66%) and that of PSA (62%) suggest that current methodology is not adequate to detect all of the patients with proven metastases. The wide range of results published in the studies cited in Table II suggests that the blood of some

TABLE II. A Comparison of Reverse Transcription-Polymerase Chain Reaction (RT-PCR) Sensitivities of Prostate-Specific Membrane Antigen (PSMA) and Prostate-Specific Antigen (PSA) in Patients with Metastatic Prostate Cancer

References	PSMA RT-PCR	PSA RT-PCR
Cama et al. [51]	10/20 (50%)	16/20 (80%)
Israeli et al. [12]	16/24 (67%)	6/24 (25%)
Grasso et al. [52]	10/11 (91%)	7/11 (64%)
Loric et al. [53]	28/33 (85%)	17/33 (51%)
Sokoloff et al. [54]	13/33 (39%)	29/33 (88%)
Zhang et al. [55]	10/11 (91%)	7/11 (64%)
Pooled sensitivity	87/132 (66%)	82/132 (62%)

patients does not contain PSMA- or PSA-expressing cells, or that sensitivity of the RT-PCR assays is not sufficient. Nevertheless, recent studies report on improved sensitivity by combining both PSMA and PSA RT-PCR [55,52]. Grasso et al. evaluated the role of a combined screening approach for nested RT-PCR of PSA and PSMA in staging 136 prostate cancer patients, including 107 patients with clinically localized disease [52]. They correlated preoperative RT-PCR results with final pathological stages and found that PSMA was a more sensitive marker than PSA in detecting circulating prostate cells ($P< 0.0001$). The combination PSA/PSMA nested RT-PCR was a better predictor of tumor extracapsular extension than initial serum PSA, clinical stage, and biopsy Gleason score [52]. Since this polymerase chain reaction (PCR) technique cannot be quantified at present, its future usefulness may be limited.

CONCLUSIONS

PSMA has contributed to identifying, staging, and monitoring metastatic prostate cancer. The development of an ELISA for accurate measurement of PSMA in body fluids has potential significance. A combination of PSMA and other prostate cancer-markers may have a synergistic effect on the management of variant types of prostate cancer. In addition, PSMA shows a promising role in directed imaging and therapy of recurrent or metastatic disease.

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